Sustainable Approaches to Novel Heterocyclic Scaffolds for Medicinal Chemistry

Robert W. Foster

University College London

2015

A thesis submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy (PhD).

Declaration

I, Robert William Foster, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Robert William Foster

13/07/2015

Abstract

This thesis investigates new methods for the environmentally sustainable synthesis of heterocyclic scaffolds for application in medicinal chemistry. Chapter I introduces general principles of sustainability in synthetic organic chemistry. This includes the characterization and application of sustainable solvents and the use of biomass feedstocks in synthesis.

Chapter II explores the synthesis of substituted isoindolinones *via* a ruthenium-catalyzed alkyne cyclotrimerization. The introduction details the synthesis and medicinal application of isoindolinones and describes previous research involving alkyne cyclotrimerizations. Following this, the development of a regioselective alkyne cyclotrimerization reaction in a sustainable solvent is reported. The optimized alkyne cyclotrimerization conditions are then used to synthesize a selection of isoindolinone products.

Chapter III describes the application of a kinetically-controlled furan-Diels–Alder reaction to the synthesis of heterocyclic scaffolds, including the *endo*-cantharimide. The study and application of furan-Diels–Alder reactions are introduced. Following this, the Diels–Alder reaction of a 3-alkoxyfuran under sustainable reaction conditions is explored experimentally and applied to the diastereoselective synthesis of *endo*-cantharimides. The potential application of *endo*-cantharimides in medicinal chemistry is discussed with the aid of biological testing and the Diels–Alder reactions of 3-alkoxyfurans is probed with the aid of computational calculations.

Chapter IV concerns the cyclization of reducing sugars to prepare chiral tetrahydrofurans. The role of tetrahydrofurans in medicinal chemistry, the synthesis of tetrahydrofurans from sugar derivatives and the application of hydrazones in synthetic chemistry are introduced. Following this the development of a hydrazone-mediated cyclization of L-arabinose under sustainable reaction conditions is reported. The optimized conditions are applied to prepare tetrahydrofurans from other sugars. The manipulation of the tetrahydrofuran products is also explored.

Chapter V draws some general conclusions from the thesis and describes potential future directions for the research. Chapter VI contains the details of experimental procedures and compound characterization for the results discussed in Chapters II–IV.

Acknowledgements

I am indebted to my academic supervisors, Dr Tom Sheppard and Professor Helen Hailes. Over the past four years Tom and Helen have ensured that I have never been left short of ideas, inspiration or encouragement. I am grateful to them both for making the time I have spent at UCL a thoroughly enjoyable and engaging experience.

Thanks to my industrial supervisor Dr Christopher Tame. I have benefited greatly from Chris' exceptional commitment to this CASE collaboration. We've come a long way since our first CASE meeting and Chris has always been a fantastic source of scientific insight and enthusiasm.

I am grateful to Dr Michael Porter for training me in the field of computational chemistry and for supervising my time as a physical organic chemist. The three months I spent running computational experiments was a valuable experience and working with Mike was a real pleasure.

As part of my PhD I spent nine months on placement with GlaxoSmithKline at the Medicines Research Centre in Stevenage. I would like to thank all of the people who made my time there such an enjoyable and productive experience. In particular, I would like to thank Dr Ian Churcher, Dr John Harling and the other members of the Protein Degradation DPU. I would also like to thank Dr Simon Peace for his valuable input.

Thanks to Dr Dejan-Krešimir Bučar and Dr Laure Benhamou for their work performing X-ray crystallographic analysis on a number of compounds. I am grateful to Dr Abil Aliev for his help in assigning numerous tricky NMR spectra. Thanks to Dr Lisa Haigh, Dr Fred Cambell, Dr Vincent Gray and Dr Kersti Karu for mass spectrometry data.

I am grateful to the Engineering and Physical Sciences Research Council, GlaxoSmithKline and UCL for funding my PhD. I would also like to thank the Royal Society of Chemistry and the Society of Chemistry and Industry for funding travel to international conferences.

I would like to thank all of those who I have worked beside over the last four years who have made my time at UCL such a fantastic experience. Thanks also to Ashley and my family for all their love and support.

Summary of Abbreviations

1,3-PDO	1,3-propane diol
2-MeTHF	2-methyltetrahydrofuran
3-HPA	3-hydroxypropanoic acid
9-BBN	9-borabicyclo[3.3.1]nonane
°C	degrees centigrade
Ac	acetyl
ACS	American Chemical Society
Ar	generic aryl group
API	Active Pharmaceutical Ingredient
aq.	aqueous
AZT	Azidothymidine
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
b.p.	boiling point
br.	broad
BSTFA	bis(trimethylsilyl)trifluoroacetamide
BTX	benzene, toluene and xylenes
CED	cumulative energy demand
Cp	η-5 cyclopentadienyl
Cp*	η-5 pentamethyl cyclopentadienyl
CPME	cyclopentyl methyl ether
^{c}Pr	cyclopropyl
cod	1,5-cyclooctadiene
conc.	concentrated
CSA	(±)-camphorsulfonic acid
Cy	cyclohexyl
D-	dextrorotatory-
Da	dalton
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMA	dimethylacetamide

DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1′-bis(diphenylphosphino)ferrocene
d.r.	diastereoisomeric ratio
EC_{50}	half maximal effective concentration
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
e.e.	enantiomeric excess
Et	ethyl
ER	estrogen receptor
ESI	Electro-Spray Ionisation
FGI	functional group interconversion
GC	glycerol carbonate
GVL	γ-valerolactone
h	hour(s)
H_8-BINAP	(*S*)-(−)-2,2′-Bis(diphenylphospino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl
HDAC	histone deacetylase
HIV	human immunodeficiency virus
HMDS	hexamethyldisilazide
HMF	hydroxymethylfurfural
hν	ultraviolet irradiation
HSQC	Heteronuclear Single Quantum Coherence
Hz	hertz
IC_{50}	half maximal inhibitory concentration
J	joule
L	generic ligand
L-	levorotatory
i	*iso*
LDA	lithium diisopropylamide
M	molar
MDM2	mouse double minute 2 homolog
Me	methyl

MMPP	magnesium monoperoxyphthalate
mol	mole(s)
Ms	methanesulfonyl
mw	molecular weight
n	*norm*
NBS	*N*-bromosuccinimide
n.d.	not determined
NMR	Nuclear Magnetic Resonance
P	partition-coefficient
p	*para*
PC	propylene carbonate
PEG	polyethylene glycol
petrol	petroleum ether
PMB	4-methoxybenzyl
Ph	phenyl
PPA	polyphosphoric acid
Ppm	parts per million
Pr	propyl
R	generic alkyl group
R_f	retention factor
ROE	Rotating-frame Overhauser Enhancement
RT	room temperature
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
SCX-2	Strong Cation eXchange cartridge
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidinyloxy
t	*tert*
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
Ts	*para*-toluenesulfonyl

Table of Contents

Chapter I. Introduction

The aim of this thesis is to explore the selective synthesis of novel heterocyclic scaffolds for medicinal chemistry using sustainable reaction conditions. This research is split into three independent areas; the synthesis of isoindolinones *via* ruthenium-catalyzed alkyne cyclotrimerizations, the synthesis of cantharimides from 3-alkoxyfurans and the transformation of reducing sugars into chiral tetrahydrofurans. This chapter will introduce the principles of sustainable organic synthesis, with a focus on the use of sustainable solvents and biomass-derived feedstocks.

1.1. Principles of Sustainable Synthetic Organic Chemistry

The twentieth century has witnessed rapid progress in the field of chemistry and a large expansion of materials and medicines that are in production. However, the manufacture of chemicals is heavily dependent on finite reserves of fossil fuels for both energy and feedstocks. Industry and governments are recognizing the importance of reducing this dependence in order to reduce the environmental damaged caused by chemical processes.

A major consumer of fine chemicals and solvents, and ultimately fossil fuels, is the pharmaceutical industry.[1] Reducing the environmental impact of drug manufacture is an important corporate goal of pharmaceutical companies.[2] For example, GlaxoSmithKline have committed to a carbon-neutral value chain by the year 2050.[3] In addition to drug manufacture, drug development is another significant source of environmental damage and addressing this is key to improving sustainability in the discovery of new medicines.[4]

1.1.1. Economy in Synthesis

Twelve Principles of Green Chemistry

An important guide to sustainability in synthesis are the Twelve Principles of Green Chemistry, proposed by Anastas and Warner (**Figure 1**).[5] In summary, they encourage the efficient use of renewable raw materials to selectively manufacture chemicals without the need for dangerous solvents, reagents and processes. This work has inspired other sustainability guides, including Winterton's Twelve More Green Chemistry Principles,[6] Anastas and Zimmerman's principles of green engineering[7] and Tang's PRODUCTIVELY pneumonic.[8]

1. *It is better to prevent waste than to treat or clean up waste after it is formed.*
2. *Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.*
3. *Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.*
4. *Chemical products should be designed to preserve efficacy of function while reducing toxicity.*
5. *The use of auxiliary substances (*e.g. *solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.*
6. *Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.*
7. *A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.*
8. *Unnecessary derivatization (blocking group, protection/ deprotection, temporary modification) should be avoided whenever possible.*
9. *Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.*
10. *Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.*
11. *Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.*
12. *Substances and the form of a substance used in a chemical process should be chosen to minimize potential for chemical accidents, including releases, explosions, and fires.*

Figure 1. Twelve Principles of Green Chemistry. Reproduced from Ref. 8 with permission from The Royal Society of Chemistry.

E Factor

A useful measure of the economy of a chemical process is the E factor (Environmental Factor), as proposed by Sheldon.[9] The E Factor is defined as the mass of the waste generated in a process divided by the mass of the product. As such, the E Factor of a process should be as close to zero as possible. In calculating a value all the raw material required to produce a product is considered, including all reagents, solvents and the fuel required. The only exception made is water (minus any organic or inorganic waste products in the aqueous extracts). While low E Factors can be achieved for petrochemical and bulk chemical processes, good economy in the pharmaceutical industry is a more challenging proposition (**Table 1**).[10]

Table 1. E Factors in chemical industries.

Industry	Product scale/tonnes	E Factor
Oil refining	10^6–10^8	<0.1
Bulk chemicals	10^4–10^6	<1–5
Fine chemicals	10^2–10^4	5–50
Pharmaceuticals	10–10^3	25–100

Reproduced from Ref. 10 with permission from The Royal Society of Chemistry.

Atom Economy

Another metric for sustainable chemistry is atom economy, as proposed by Trost.[11] It is defined as the molecular weight of a product divided by the sum of the molecular weight of all substances formed for a reaction process. Atom Economy does not account for catalysts, solvent, excess reagent, reaction yield or the provenance of reagents but is a very straightforward method to quantify the efficiency of a process. Various other concepts have been proposed to quantify the economy of a synthesis,[12] including process mass intensity,[13] reaction mass efficiency[14] and molar efficiency.[15]

1.1.2. Sustainable Solvents

The biggest individual source of waste in the manufacture of active pharmaceutical ingredients (APIs) is solvent. A study by Henderson *et al.* of the waste generated by GlaxoSmithKline in the production of APIs concluded solvent was responsible for *ca.* 85% of the non-aqueous waste generated by mass (**Figure 2**).[16] As such, the most effective way to reduce the environmental impact of a manufacturing process is very often to address the waste associated with the use of solvent.

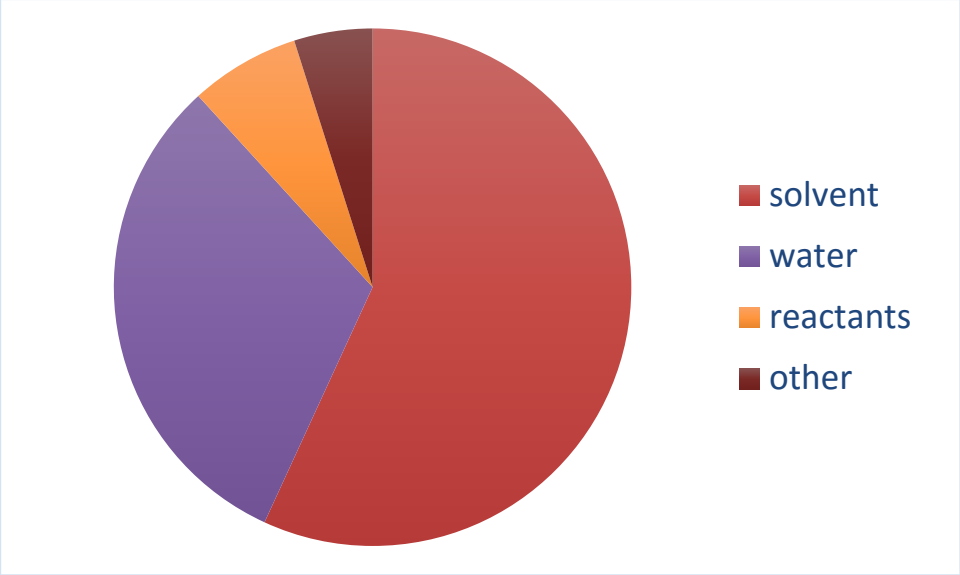


Figure 2. Material inputs by mass for the synthesis of an active pharmaceutical ingredient.[16]

Ideally reactions should be conducted without solvents or conducted in water to minimize the environmental waste.[17] However, it is rarely possible to eliminate organic solvent from a synthesis and consideration must be given to which solvents should be used to minimize environmental impact. Other issues such as occupational health and safety, which are not directly related to environmental impact, are also often taken into consideration when rating solvents for their use in organic synthesis. A summary of these factors is given below.

Manufacture

The industrial production of solvent in an energy intensive process and is often dependent on the use of fossil fuels.[18] Fischer *et al*.[19] have calculated the cumulative energy demand (CED) for the manufacture of a series of common solvents, including those represented in **Figure 3**. It is notable that the energy required to manufacture THF is significantly greater than that required to manufacture a solvent like MeOH. This is in part because the synthesis of THF requires multiple steps, whereas MeOH can be prepared in a single step from synthesis gas.[18]

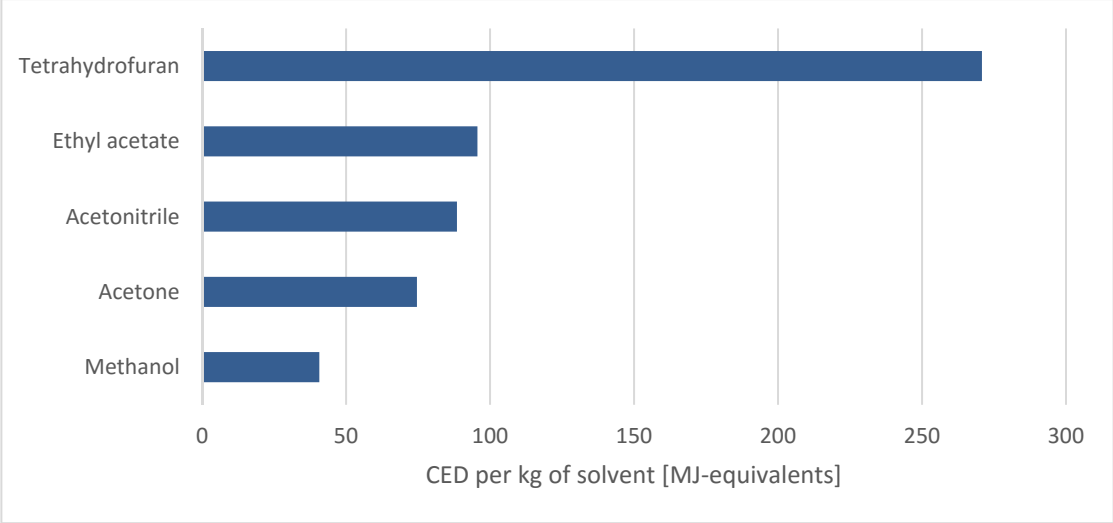


Figure 3. Energy required to manufacture organic solvents.[19]

Disposal and Recovery

Non-aqueous solvent is typically disposed by incineration and there are two important factors that determine how economical this is. Firstly, the disposal of chlorinated solvents is more expensive because they are typically non-flammable and so fuel must be consumed during incineration. In addition, if a solvent cannot be effectively separated from an aqueous extract then the aqueous extract must also be incinerated. This is a significant problem for solvents like THF that are only partly miscible with water.

One method to potentially improve the economy of a process is to recover the solvent at the end of a reaction through distillation and there are a number of factors that have an impact on how straightforward this may be. Ideally a solvent will not have a very high boiling point (to minimize energy use), not have a boiling point within 10 °C of many other solvents (to aid separation) and would not form an azeotrope with many other solvents. A low explosive/ flammability risk is also important for safe solvent recovery, as is good solvent stability. Although solvent distillation can be an energy-intensive process, an analysis of twenty six common solvents by Fisher *et al.* concluded that distillation was generally environmentally superior to incineration.[19]

Pollution

In addition to the carbon dioxide produced in the manufacture, recovery and disposal of solvent, there are also a number of other means by which the use of a solvent may result in environmental damage. Many organic solvents are classified as Volatile Organic Compounds (VOCs), which are known to reduce air quality when they evaporate. Solvents such as carbon tetrachloride and 1,1,1-trichloroethane pose a risk to the ozone

layer, and are subject to strict regulation.[20] In addition, many solvents pose a risk to aquatic life. For example, solvents such as limonene, cyclohexane and dichlorobenzene are known to be very toxic to aquatic life and potential causes of long-term damage to the aquatic environment.

Occupational Health

A number of commonly used solvents posse an established or potential occupational health hazard. Solvents such as benzene and 1,2-dichloroethane (DCE) are known carcinogens while dimethylformamide (DMF), *N*-methyl-2-pyrrolidone (NMP) and 2-methoxyethanol are possible reproductive toxins.

Patient Safety

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use have set limits on the presence of specific solvents in clinical medicines.[21] While solvent such as EtOH, acetone and DMSO may be present at 5000 ppm the limit on benzene in 2 ppm. Consequently, the Food and Drug Administration recommend that benzene along with CCl_4, 1,1-dichloroethane and 1,2-dichloroethane are avoided in the synthesis of pharmaceutical agents on the grounds of patient safety.

Occupational Safety

There are numerous safety risks associated with the storage and use of organic solvents. The flammability risk is associated with physical properties such as the flash point, boiling point, autoignition temperature, electrical conductivity and vapor pressure. Rare solvents such as nitromethane pose an additional risk of explosions. Solvents such as THF are liable to form peroxides over time, which presents an additional explosive hazard unless special precautions are taken. Other solvents possess specific safety hazards. For example, AcOH can cause severe burns on contact with skin.

By considering these factors it is possible to assess solvents based on their environmental credentials.[22] To date GlaxoSmithKline,[23] AstraZeneca,[24] Pfizer,[25] Sanofi[26] and the ACS Green Chemistry Institute Pharmaceutical Roundtable[27] have all produced solvent guides to aid synthetic chemists. The summarized version of the GlaxoSmithKline Solvent Selection Guide is given in **Figure 4** as a representative example. There are also solvent guides for specific transformations, which aim to replace traditional solvents with poor environmental profiles with more sustainable alternatives.[28]

Figure 4. GlaxoSmithKline solvent selection guide. Reproduced from Ref. 23 with permission from The Royal Society of Chemistry.

With the need to find alternatives to many traditional solvents with poor environmental properties, a number of compounds have recently been publicized as alternative green solvents. Examples include 2-MeTHF,[29] cyclopentyl methyl ether (CPME),[30] dimethyl carbonate (DMC),[31] propylene carbonate (PC),[32] γ-valerolactone (GVL),[33] glycerol,[34] polyethylene glycol (PEG),[35] piperylene sulfone[36] and supercritical carbon dioxide.[37] Ionic liquids have also been promoted as green solvents,[38] although they can require significant resources to manufacture[18] and exhibit acute toxicity to aquatic organisms.[39] A particular challenge is to produce new sustainable solvents with similar properties to the established solvents which need to be avoided.[18]

1.1.3. The Application of Biomass in Chemical Synthesis

The majority of carbon-based organic compounds manufactured by the chemical industry are derived directly from petroleum.[40] With the supply of readily accessible oil dwindling, the scientific community has turned its attention to the use of biomass as an alternative feedstock for synthetic chemistry.[41]

It is estimated that annually the Earth produces 10^{11} tonnes of biomass, of which only 3% is harvested for human consumption.[42] Human activity (such as agriculture and manufacturing) produces a significant quantity of biomass as waste and so it is a potentially ideal resource for the production of small molecules, materials and fuels.[43] The majority of biomass (75%) is composed of carbohydrates such as cellulose, hemicellulose, chitin, starch, inulin and sucrose (**Figure 5**). Lignocellulose accounts for 20% of biomass, and comprises *ca*. 65% cellulose and hemicellulose and *ca*. 20% lignin. The remaining 5% of biomass is accounted for by proteins, terpenes and triglycerides.

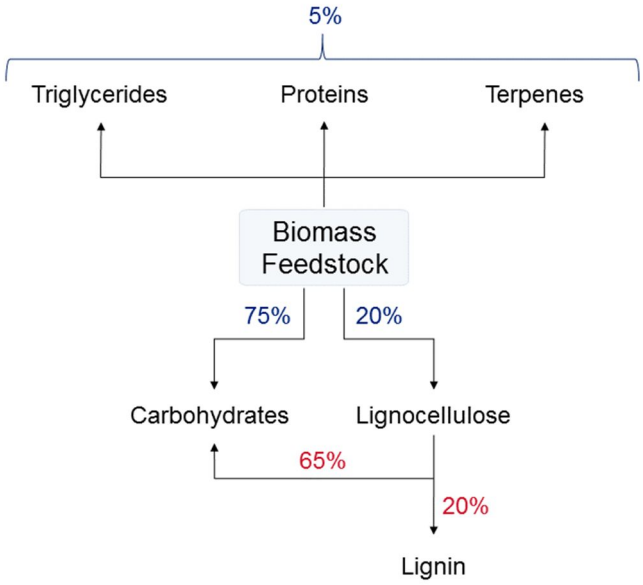
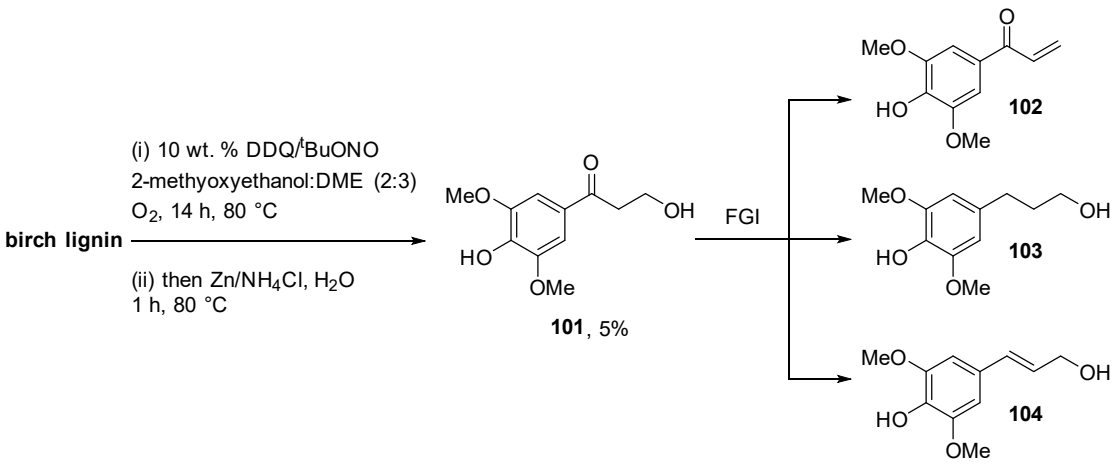


Figure 5. The composition of biomass feedstock.[42]

Lignin is an abundant biopolymer that has been widely studied as a potential source of aromatic compounds.[44] Lignin is typically extracted from lignocellulose by pre-treatment with water under high temperature and pressure followed by treatment with glycoside-degrading enzymes.[45] However, the production of small molecules from lignin has proved extremely challenging and the majority of lignin produced as a by-product of the pulping industry is still burned as a fuel.[43] There have been a number of recent advances in this area,[46] including Westwood's synthesis of small aromatic building blocks from birch lignin (**Scheme 1**).[47]

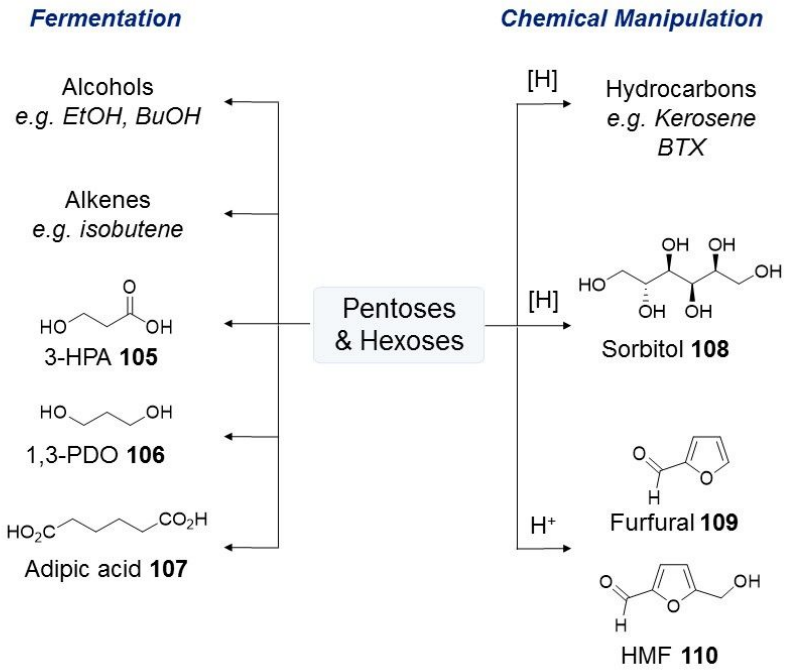


Scheme 1. Westwood's synthesis of aromatic small molecules from birch lignin.[47]

Carbohydrates make up the greatest constituent of biomass and have also been investigated as a source for high-value small molecules.[42] Agricultural biomass is typically 30–40% cellulose, a regular polysaccharide of D-glucose. An additional 20–30%

is comprised of hemicellulose; an irregular carbohydrate formed from multiple polysaccharides. The composition of hemicellulose varies, but is mostly comprised of xylose, mannose, galactose, arabinose and rhamnose. Both cellulose and hemicellulose can be cleaved to give the component monosaccharides either under acidic conditions or using enzymes.[48]

There are multiple methods to transform the carbohydrates that can be sourced from cellulose and hemicellulose into valuable small molecules (**Scheme 2**).[49] An industrially attractive method is fermentation and this has been used to access a series of platform chemicals that are traditionally prepared by the petrochemical industry. The fermentation of sugars to form EtOH is an age-old approach that has been adapted into an industrial process, with production reaching *ca.* 99 million tonnes in 2010.[50] This process has been adapted for the formation of ^{n}BuOH through the engineering of recombinant microorganisms.[51] Dehydration of these compounds also allows access to bio-ethylene and bio-butene, both valuable intermediates in the bulk chemical industry[52]. It is additionally possible to access olefins such as isobutene and butadiene directly through the fermentation of sugars.[53] Other compounds which can be accessed through fermentation include 3-hydroxypropanoic acid (3-HPA) **105** (a precursor to acrylic acid),[54] 1,3-propane diol (1,3-PDO) **106** (a building block for the polyester polytrimethylene terephthalate)[55] and adipic acid **107** (a component of nylon).[56]

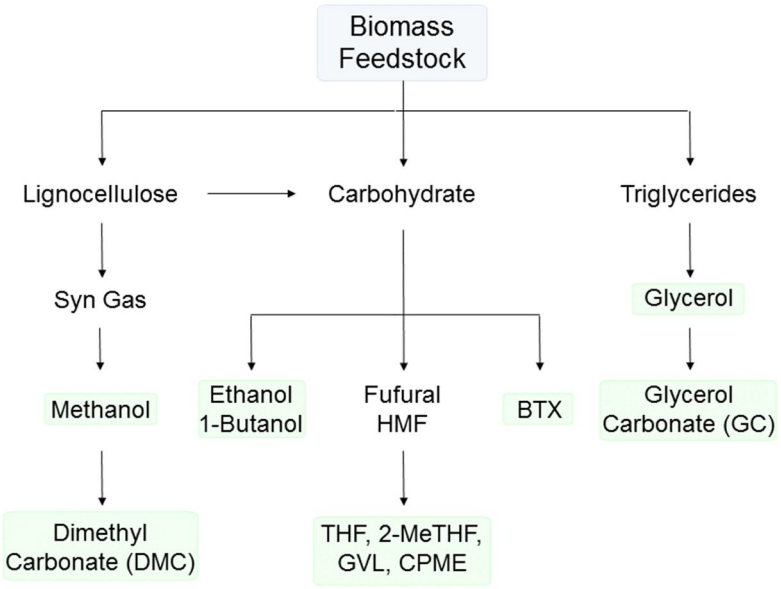


Scheme 2. Synthesis of platform chemicals from carbohydrates.

Another valuable method for transforming carbohydrates is *via* chemical manipulation (**Scheme 2**). Reducing pentoses and hexoses using hydrogen gas and heterogeneous catalysts can yield a variety of hydrocarbons,[57] such as benzene, PhMe and xylenes (BTX).[58] A selective reduction of D-glucose gives sorbitol **108**, which is used as a food sweetener and as an intermediate for the synthesis of fuels, materials and pharmaceutical agents.[59] Dehydration of pentoses and hexoses under acidic conditions respectively yields furfural **109** and hydroxymethylfurfural (HMF) **110**.[60] These versatile intermediates have both been exploited for the synthesis of small-molecule building blocks,[61] fuels,[62] surfactants[63] and bioactive compounds.[64]

An important use for biomass-derived compounds is as organic solvents (**Scheme 3**). As described previously, solvent is typically the biggest input for the synthesis of pharmaceutical agents and therefore using renewably-sourced solvent is an effective way to improve the sustainability of a manufacturing process. For example, MeOH can be prepared from synthesis gas, which can in turn be prepared by gasification of lignocellulose.[42] This can then be converted into dimethyl carbonate (DMC) through reaction with carbon monoxide and oxygen.[65] As discussed above, higher alcohols such as EtOH and ^{n}BuOH can be prepared by fermentation of carbohydrates.[50] Carbohydrates can be converted into a variety of alcohols and hydrocarbons including some well-

established solvents. Carbohydrates can also be converted into furfural and HMF, which can be transformed into various solvents,[66] including THF,[67] 2-MeTHF,[68] γ-valerolactone (GVL)[69] and cyclopentyl methyl ether (CPME).[70] Biomass feedstock is also a source of triglycerides, which can be hydrolyzed to give glycerol.[42] Both glycerol[34] and glycerol carbonate (GC) [71] have been proposed as sustainable solvents.



Scheme 3. Preparing solvents from biomass.

1.2. Summary and Project Aims

The better management of natural resources and the reduction of environmental damage is critical to the future of the chemical industries. For the synthesis of pharmaceutical agents, the biggest cause of waste and environment damage is from the use, recovery and disposal of organic solvent. As such it is essential to expand the use of solvents with more sustainable properties and avoid those that are known to have serious environmental issues. It is also important to make better use of those resources that can be sourced sustainably from biomass, whether that be as solvents or molecular building blocks. This is essential not only for the sustainable manufacture of existing medicines but also for the sustainable discovery of new drugs.

The aim of this project is to develop sustainable methodologies for the synthesis of novel heterocyclic scaffolds for medicinal chemistry. Efficiency is key to a successful synthetic strategy, in terms of step-count, selectivity and yield. For medicinal chemistry it is important that methodologies are designed for the rapid preparation of compound libraries, using either convergent or divergent approaches. Substrate scope is also

essential in this regard. Finally, the principles of sustainable synthesis discussed in this chapter must be closely considered in developing new synthetic methods, in order to reduce the environmental impact.

Chapter II. Highly Regioselective Synthesis of Substituted Isoindolinones *via* Ruthenium-Catalyzed Alkyne Cyclotrimerizations

2.1. Introduction

2.1.1. The Application of Isoindolinones in Medicinal Chemistry

The isoindolinone skeleton has been applied widely within medicinal chemistry to develop compounds with activity against a range of biological targets, with examples given in **Figure 6**. Miyachia *et al.* developed hydroxamic acid **201** as a novel histone deacetylase (HDAC) inhibitor which exhibited improved activity over clinically used HDAC inhibitor Zolinza.[72] Hardcastle *et al.* reported substituted isoindolinone **202** as a potent MDM2-p53 protein–protein interaction inhibitor (IC_{50} = 44 ± 6 nM), with a potential application as an antitumor agent.[73] In addition, isoindolinone **203** was developed by Kawanishi *et al.*[74] and has been shown to be a selective inhibitor of cyclin-dependent kinase subtype 1 while Spicer *et al*.[75] reported isoindolinone **204** as a cytolytic protein perforin inhibitor. Medicinal chemists have developed substituted isoindolinones with biological activity against a variety of other targets[76] including the α1-adrenoceptor,[77] DNA gyrase,[78] dopamine D2 and D4 receptors,[79] hypoxia-inducible factor-1α,[80] metabotropic glutamate subtype 2 receptor[81] and tumor necrosis factor-α.[82] The isoindolinone motif also forms the core of a wide selection of natural products.[83]

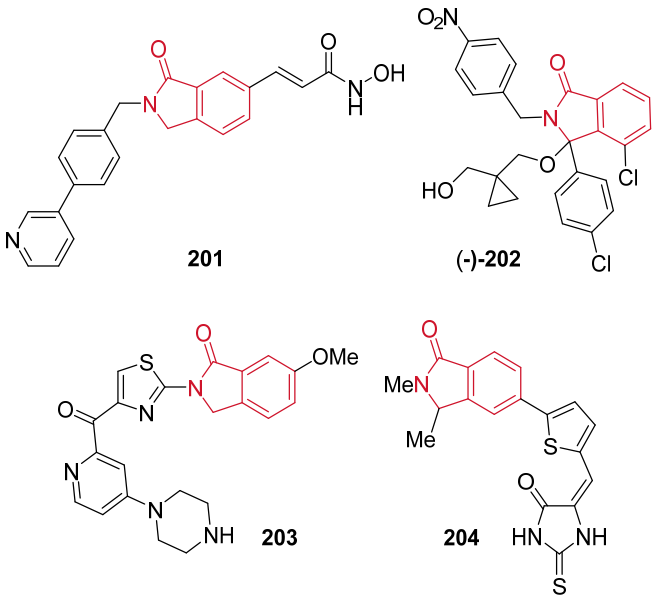
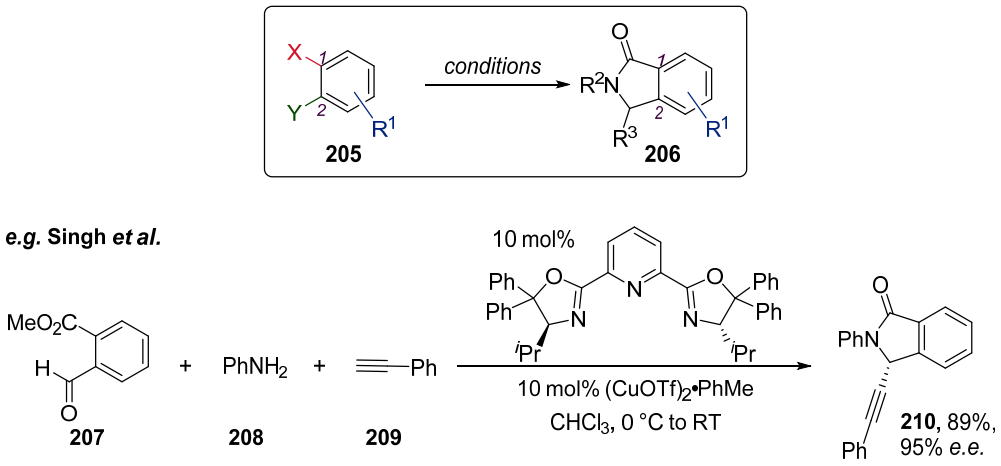


Figure 6. Examples of bioactive isoindolinones within medicinal chemistry.

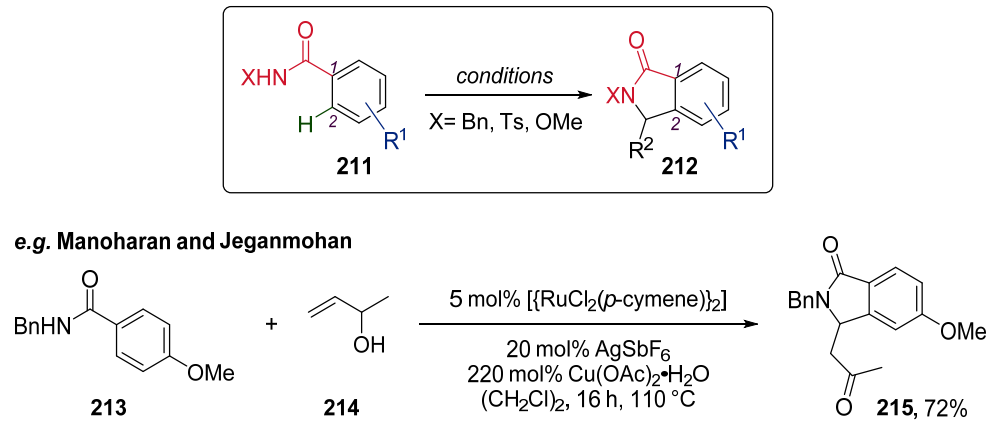
2.1.2 Synthetic Approaches to Substituted Isoindolinones

The regio- (and stereo-) selective synthesis of substituted isoindolinones has recently generated significant interest within the scientific community. This work has primarily focused on the generation of isoindolinones from a pre-formed aromatic ring with two adjacent substituent (X and Y, **Scheme 4**) that are transformed into a lactam. This general approach has been developed for a wide range of substrates to access different substituted isoindolinones products.[84] A variety of catalysts have been used including copper,[85] palladium,[86] nickel,[87] rhodium,[88] KO^{t}Bu,[89] platinum nanowires,[90] phase-transfer catalysts,[91] chiral amines[92] and NBu_4OAc.[93] A notable example is the Cu(I)-catalyzed alkynylation/lactamization cascade to convert benzaldehyde **207** into 3-alkynyl isoindolinone **210** with excellent stereocontrol, as reported by Singh *et al*. (**Scheme 4**).[94]



Scheme 4. General approach to isoindolinones from 1,2-disubstitued benzenes and an example from Singh *et al.*[94]

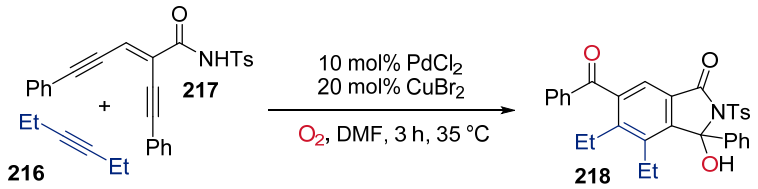
Another important route to substituted isoindolinones is *via* C-H activation strategies (**Scheme 5**). This has been achieved using benzamide derivatives *via* palladium,[95] rhodium,[96] nickel[97] and ruthenium catalysis.[98] For example, Manoharan and Jeganmohan reported a ruthenium-catalyzed synthesis of isoindolinone **215** from benzamide **213** using a super-stoichiometric copper(II) oxidant and alcohol **214** (**Scheme 5**).[99] Additionally, Smith *et al.*[100] have reported a similar approach to isoindolinones *via* directed lithiation of a substituted arene using stoichiometric ^{t}BuLi and Nakata *et al.*[101] developed a synthesis of isoindolinones from isopropyl benzyl carbamates using a Bischler–Napieralski-type cyclization.



Scheme 5. General synthesis of isoindolinones using C-H activation and an example from Manoharan and Jeganmohan.[99]

A much less explored route to isoindolinones is to prepare the heterocyclic core from aliphatic precursors.[102] An example of such a strategy was reported by Ma *et al.* (**Scheme 6**).[103] Their approach was based on a palladium/copper-catalyzed oxidative cyclization of enediyne **217** and internal alkyne **216** to give the highly substituted isoindolinone **218**,

although regioselectivity was generally poor when the alkyne was non-symmetrical. In general this approach of generating an aromatic core from linear precursors allows for a more convergent approach to substituted isoindolinone products.



Scheme 6. Synthesis of isoindolinones from enediyne 217 and alkyne 216 by Ma *et al.*[103]

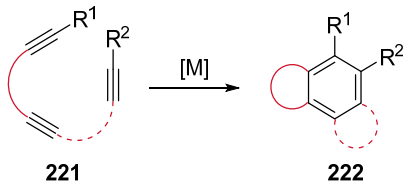
2.1.3. Synthesis of Aromatic Compounds *via* Alkyne Cyclotrimerization Reactions

In 1948 Reppe *et al.*[104] reported the first transition metal-catalyzed [2+2+2]-cyclotrimerization of alkynes to form substituted benzenes. Since then, alkyne cyclotrimerizations have been used to make densely functionalized aromatic compounds using a large range of transition metal catalysts (**Scheme 7**).[105] Alkyne cyclotrimerizations offer a convergent and atom economical route to highly substituted unsaturated compounds from readily accessible starting materials. Traditionally, polysubstituted benzene rings are often prepared *via* electrophilic aromatic substitution, a synthetic strategy which typically requires multiple steps, the use of protecting groups, functional group interconversion and a careful choice of conditions to ensure good regioselectivity.[106] Directed metalation is another widely used technique for aromatic substitution,[107] but it is inherently limited by its nature.[106] As such alkyne cyclotrimerization offers an attractive alternative to these more conventional techniques.

Scheme 7. Alkyne cyclotrimerization reaction.

The main synthetic challenge associated with alkyne cyclotrimerizations is that of regioselectivity. The homo-trimerization of a terminal alkyne will typically give a mixture of 1,2,4- and 1,3,5-trisubstituted benzenes, while attempting a 3-component hetero-trimerization can yield over 30 different products.[108] Examples of highly selective multicomponent [2+2+2]-cycloadditions have been reported but they are limited in

substrate scope.[109] A more successful and general strategy for selective [2+2+2]-cyclization is to link 2 or 3 π-components with an organic linker (**Scheme 8**), as was pioneered by Vollhardt *et al.*[110] The strategy of tethering relies on the lower entropy of activation associated with intramolecular processes and has been applied to the synthesis of a wide range of products. However, it does not always eliminate side reactions as the intermolecular cyclization of tethered components is often observed.[111]



Scheme 8. Tethered alkyne cyclotrimerization.

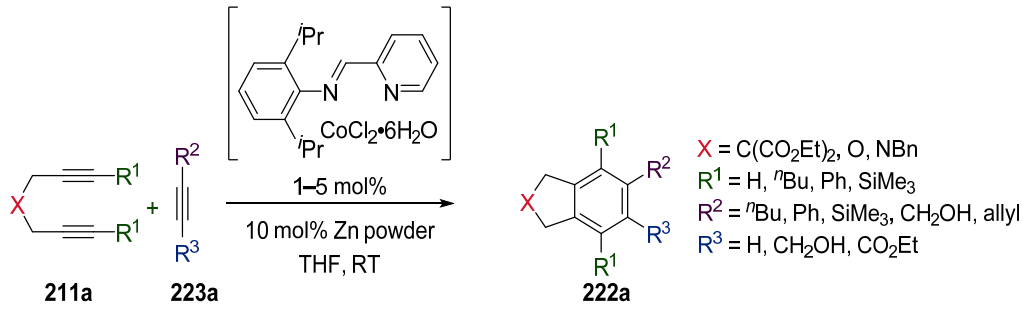
The cyclotrimerization of alkynes has been reported with an extensive number of organometallic catalysts, each with their own distinct reaction scope.[105f] The metals which have been most widely studied in this field are cobalt, rhodium, iridium and ruthenium.[105f]

Cobalt Catalysis

Much of the initial work on alkyne cyclotrimerizations was developed using $CoCp(CO)_2$ under visible light irradiation. Vollhardt developed a lot of this early chemistry[110] and applied it to the synthesis of B ring aromatic steroids.[112] More recently, $CoCp(CO)_2$ has been exploited by Malacria *et al.*[113] in the synthesis of the taxoid core, by Elwahy and Hafner in the synthesis of 1,2,4-tris(azulen-1-yl)benzenes[114] and by Siebert *et al.* in the cyclotrimerization of diborylacetylenes to give hexaborylbenzene derivatives.[115] Although $CoCp(CO)_2$ has proved popular for the cyclotrimerization of alkynes, its use typically requires heating of the reaction in xylene at reflux, the strict exclusion of oxygen and sometimes a stoichiometric amount of the metal complex.[105f]

Cheaper catalytic systems based on cobalt halides have been developed.[105f] In 2006, Okamoto *et al.*[116] reported a general synthesis of aromatic compounds using a low-cost cobalt catalyst and Zn dust in THF at 40 °C (**Scheme 9**). The reaction conditions were used to cyclize 1,6-diynes with a wide range of monoynes in good yield and with good functional group tolerance to give highly substituted benzenes **222a**. Additionally the reaction of a terminal monoyne with a mono-substituted diyne proceeded with good regioselectivity. Okamoto was also able to demonstrate the homo-trimerization of alkynes

and the intramolecular cyclization of triynes with some success. Okamoto later reported that adding a substoichiometric quantity of a silver salt to the catalytic system significantly improved reaction rate and substrate scope.[117] This chemistry has since been applied to the synthesis of polymers[118] and anthracenes.[119]

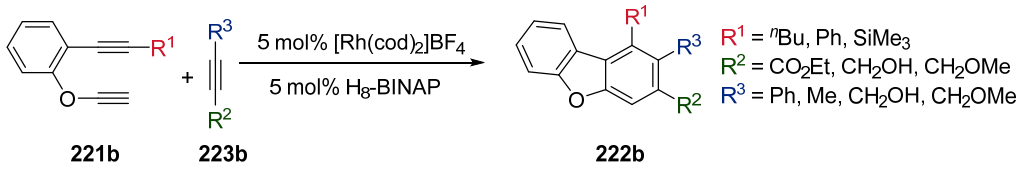


Scheme 9. Okamoto's alkyne cyclotrimerization using a low-cost cobalt complex.[116]

Rhodium Catalysis

Rhodium-catalyzed alkyne cyclotrimerizations were pioneered by Muller,[120] who used $RhCl(PPh_3)_3$ to form rhodacyclopentadienes from tethered diynes that formed substituted benzenes upon treatment with monoynes. In 1982 Griggs *et al.*[121] were the first to report the catalytic use of $RhCl(PPh_3)_3$ for cyclotrimerizations and since then it has been widely used in organic synthesis.[105h] Recent examples of note include Sun's alkyne cyclotrimerizations on a polymer support,[122] Siegel's synthesis of highly substituted fluoranthenes and indenocorannulenes[123] and Ramana's total synthesis of (–)-bruguierol A.[124]

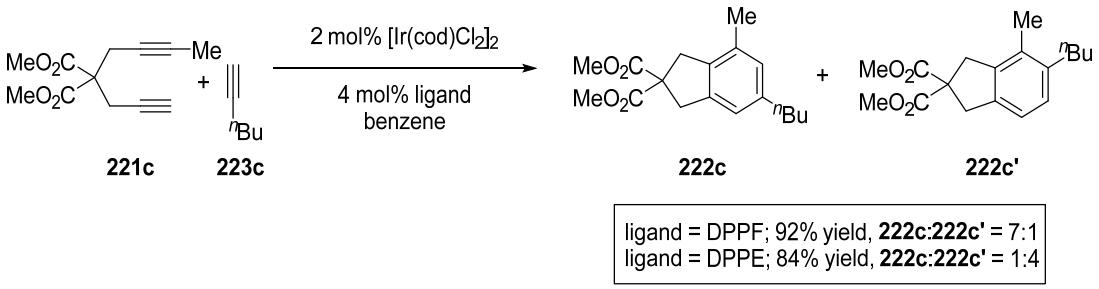
More recently cationic rhodium complexes have become popular catalysts for cyclotrimerizations.[105h] Tanaka *et al.*[125] reported the first benzofuran synthesis *via* an alkyne cyclotrimerization, using $[Rh(cod)_2]BF_4$ in combination with H_8-BINAP (**Scheme 10**). Although yields were generally reasonable it was limited by poor regioselectivity. It was also necessary to pre-activate the catalyst using hydrogen gas. Chiral cationic rhodium complexes have been widely used in the enantioselective synthesis of chiral aromatic compounds,[105h] including axially chiral biaryls,[126] *P*-stereogenic alkynyl phosphine oxides[127] and chiral aryl amides.[128] Cationic rhodium catalysis has also been used in the synthesis of polyether cyclophanes and aryl boramides.[129]



Scheme 10. Tanaka's synthesis of benzofurans *via* rhodium-catalyzed alkyne cyclotrimerizations.[125]

Iridium Catalysis

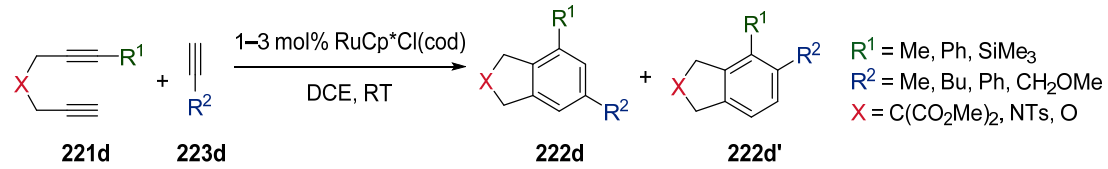
Kezuka *et al.*[130] have established $[Ir(cod)Cl]_2$/DPPE as a robust and efficient catalyst for tethered alkyne cyclotrimerizations. They reported the cyclizations of a broad range of monoynes with 1,6-diynes with good functional group tolerance. Most significantly Kezuka reported reasonable regioselectivity for the reaction of a non-symmetrical diyne and a terminal monoyne, which could be reversed with the choice of ligand (**Scheme 11**). Iridium catalysis has been employed in a number of other alkyne cyclotrimerizations,[131] which include Murakami's synthesis of Silafluorenes[132] and Shibata's synthesis of axially chiral teraryl compounds.[133]



Scheme 11. Kezuka's ligand-controlled regioselective cyclotrimerization of a non-symmetrical diyne and a terminal monoyne.[130]

Ruthenium Catalysis

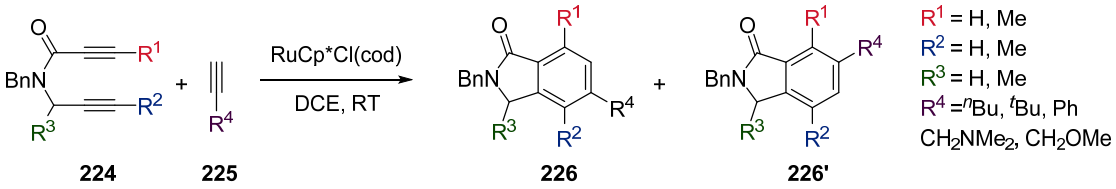
Both Grubbs' first generation catalyst[134] and Hoveyda–Grubbs' catalyst[135] have been used to efficiently mediate alkyne cyclotrimerizations, albeit with limited substrate scope. Another ruthenium complex that can catalyze cyclotrimerizations is RuCp*Cl(cod).[136] Yamamoto and Itoh demonstrated the cyclization of a range of monoynes with different 1,6-diynes using RuCp*Cl(cod) in DCE at RT (**Scheme 12**). Good regioselectivity was reported for the cycloaddition of terminal alkynes with non-symmetrical 1,6-diynes, especially when the diyne possessed a terminal trimethylsilyl substituent.



Scheme 12. Regioselective ruthenium-catalyzed cyclotrimerization of a non-symmetrical diyne and a terminal monoyne.[136a]

2.1.4. Synthesis of Isoindolinones *via* Alkyne Cyclotrimerizations

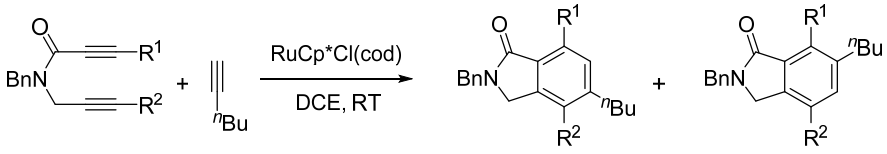
In 2004 Yamamoto *et al.* reported the first use of an amide tether for an alkyne cyclotrimerization to give an isoindolinone product (**Scheme 13**).[137] The cyclization was effective with five different monoynes and it was additionally possible to introduce a methyl group at the propargylic position of the tether (*i.e.* R^3 = Me) without complication. The cycloaddition of amide-tethered diynes with ethyl cyanoformate and propyl isocyanate was later reported as a synthesis of pyridines and pyridones.[136g]



Scheme 13. Synthesis of isoindolinones from amide-tethered diynes.[137]

Yamamoto *et al.* demonstrated that a key challenge of using amide-tethered diynes for alkyne cyclotrimerization reactions was controlling the regioselectivity (**Table 2**).[137] The authors observed that the cyclotrimerization of an amide-tethered diyne with R^1 = H preferentially formed isoindolinone **229** over its regioisomer **229'**, in the ratio 2:1 (Entry 1). This regioselectivity was reinforced by a terminal methyl substituent β to the carbonyl (R^1 = Me), with only isoindolinone **229** observed (Entry 2). Where the steric influence of a methyl substituent opposed the electronic influence of the amide (R^1 = H, R^2 = Me) the steric effect was dominant, with a product ratio **229**:**229'** of 1:4 (Entry 3).

Table 2. Regioselectivity in the cyclotrimerization of amide-tethered diynes 227 and 1-hexyne 228.[137]

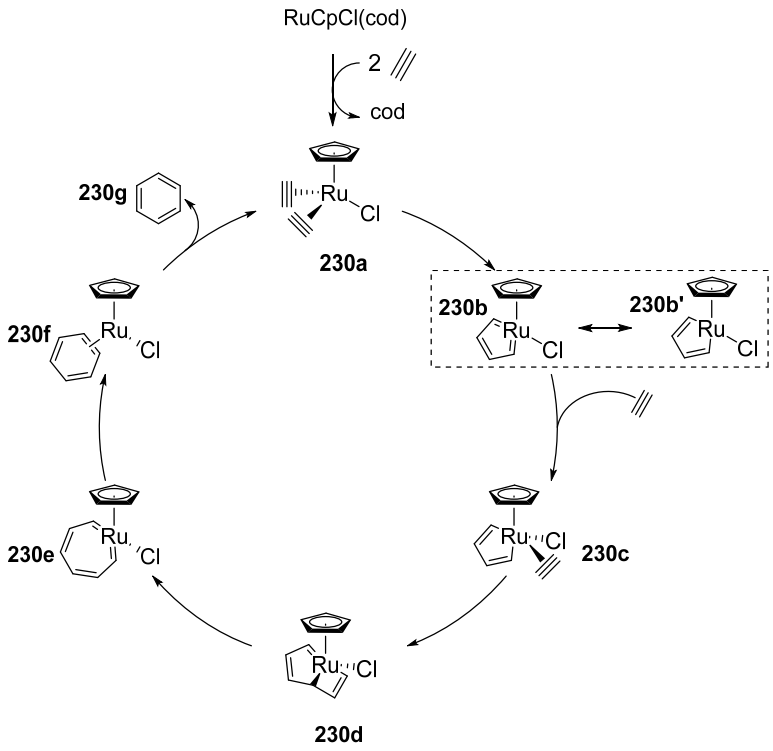


227 **228** **229** **229'**

Entry	R^1	R^2	RuCp*Cl(cod)/ mol%	Time/ h	Yield (**229** and **229'**)/ %	**229**:**229'**
1	H	H	1	0.5	76	2:1
2	Me	H	1	0.5	81	**229** only
3	H	Me	5	2	68	1:4

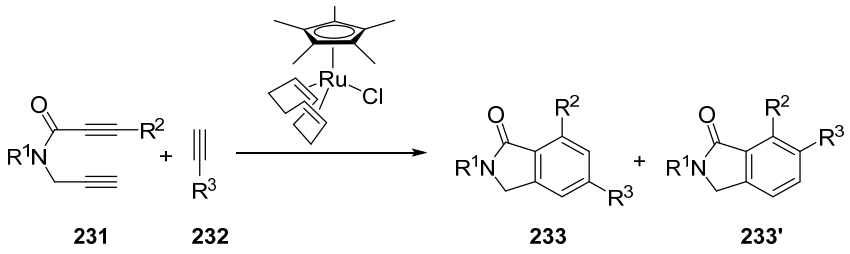
2.1.5. Mechanisms for RuCpCl(cod)-Catalyzed Alkyne Cyclotrimerizations

Alkyne cyclotrimerizations are believed to proceed *via* a number of distinct mechanisms, subject to the catalyst, ligands and substrate. One example that has been studied in detail with the aid of density functional calculations is the [RuCpCl]-catalyzed cyclotrimerization of acetylene (**Scheme 14**).[136c, 138] The 1,5-cyclooctadiene (cod) ligand of RuCp(cod) is believed to be readily displaced by two molecules of acetylene. This gives intermediate complex **230a** that can then undergo an oxidative cyclization to form ruthenacyclopentatriene **230b**, in what is believed to be the rate determining step.[138] X-ray crystal structures of analogous ruthenacycles have been acquired, and the C-C and Ru-C bond lengths are consistent with the aromatic biscarbene structure **230b**, as opposed to its canonical structure **230b'**.[136b] Complex **230b** is capable of coordinating with a third molecule of acetylene to form ruthenacyclopentadiene **230c**. It has been calculated that complex **230c** can isomerize to form ruthenabicyclo[3.2.0]heptatriene **230d** with an activation energy of only 0.4 kJ mol^{-1}.[136c] Intermediate **230d** can then ring-open to form 7-membered ruthenacycle **230e**, which on reductive elimination gives η^2-benzene complex **230f**.[138] Finally, displacement of benzene **230g** and coordination of two new molecules of acetylene regenerates catalytically active complex **230a**.



Scheme 14. Reaction mechanism for a [RuCpCl]-catalyzed alkyne cyclotrimerizations.[136c, 138]

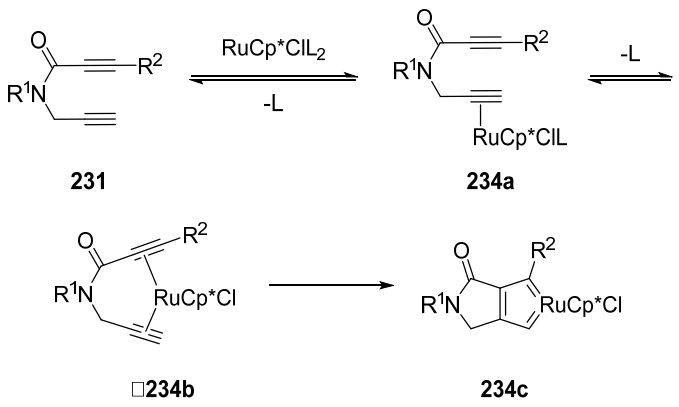
For the cyclization of non-symmetrical alkynes a question of regioselectivity may arise. Yamamoto *et al*.[137] reported the RuCp*Cl(cod)-catalyzed regioselective cyclization of an amide-tethered diyne and a monoyne (**Scheme 15**) and evaluated possible mechanistic pathways. They assumed that, mechanistically, [RuCp*Cl] would behave in a similar manner to [RuCpCl].



Scheme 15. Regioselective alkyne cyclotrimerization of amide-tethered diyne 231 and monoyne 232.[137]

As previously discussed, the cod ligand of the RuCp*Cl(cod) precatalyst is readily displaced by two neutral electron donors, such as the alkyne units of the starting material (**Scheme 16**). The terminal alkyne of the diyne is a better ligand than the internal alkyne as it is sterically less hindered and it is not electronically deactivated by an adjacent carbonyl. Once the terminal alkyne reversibly coordinates to Ru, the internal alkyne can coordinate to the metal to form bidentate complex **234b**. This can then undergo a

cyclization, which is presumed to be the rate determining step. In general, only the diyne will cyclize with the active catalyst to form ruthenacyclopentatriene **234c** as the amide tether holds the two alkynes in a reactive conformation, lowering the entropy of activation for the reaction.



Scheme 16. Formation of ruthenacycle 234c.

Once formed, the ruthenacyclopentatriene **234c** can undergo a [2+2]-addition with a third alkyne. If R^2 = H then the regioselectivity of this addition will be governed by electronic effects. Yamamoto *et al.*[137] used natural bond orbital calculations to determine natural charge for the ruthenacyclopentadiene **235** in **Figure 7**. A blue color indicates a decrease in the natural charge relative to an unsubstituted ruthenacycle while a red color indicates an increase. They demonstrated that the impact of the pyrrolidinone was to increase electron density of C-4 and decrease it at C-2. They proposed that an increase in charge at a carbon adjacent to the metal would accelerate the [2+2]-addition at that position, and this was consistent with experimental observation.

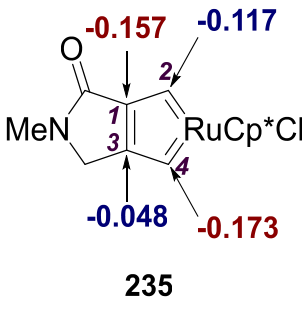
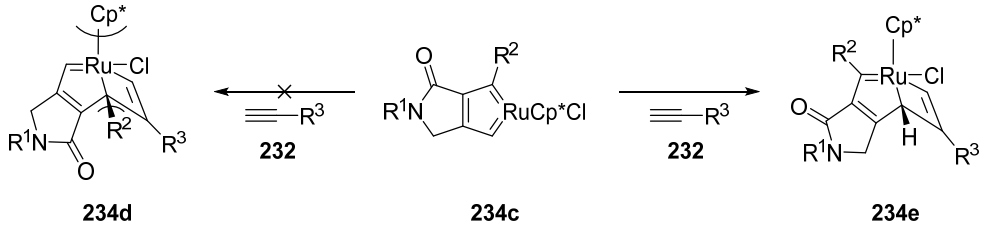


Figure 7. Pyrrolidinone ruthenacyclopentadiene 235 bearing calculated natural charges.[137]

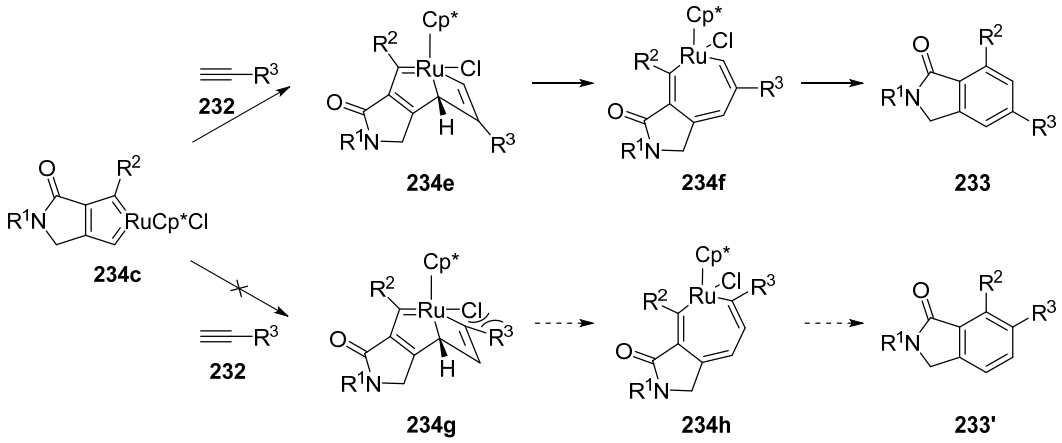
In cases where $R^2 \neq$ H, steric effects reinforce the electronic-based regioselectivity. If a [2+2]-addition occurs β to the carbonyl then the terminal alkyne substituent R^2 is forced above the plane of the pyrrolidinone (**Scheme 17**). This is sterically unfavorable as R^2 clashes with the bulky Cp* ligand. The alternative cycloaddition gives a sterically less

strained intermediate, such as complex **234e**. Consequently, addition into the Ru=C bond that is distal to the R^2 substituent has a lower kinetic barrier.



Scheme 17. Selectivity for the addition of monoyne 232 to ruthenacyclopentatriene 234c.

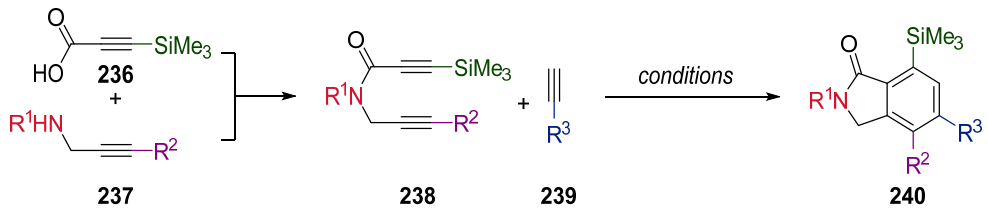
Having established the metal-carbon bond over which the [2+2]-cycloaddition occurs, it is also necessary to consider the orientation in which the incoming alkyne reacts. As is shown in **Scheme 18**, the cycloaddition can occur to form either complex **234e** or **234g**. The steric clashing between the chloride ligand and R^3 means that formation of complex **234g** is kinetically less favorable than the formation of its regioisomer **234e**. Complex **234e** isomerizes to form metallacycle **234f**, which gives isoindolinone **233** upon elimination of the catalytic species.



Scheme 18. Regioselective addition of monoyne 232 to ruthenacyclopentatriene 234c.

2.1.6. Chapter II Project Outline

The aim of this part of the PhD was to develop a novel approach to highly-substituted isoindolinones based upon a regioselective alkyne cyclotrimerization (**Scheme 19**). This would allow for the rapid and convergent assembly of isoindolinone products from readily available alkyne precursors.



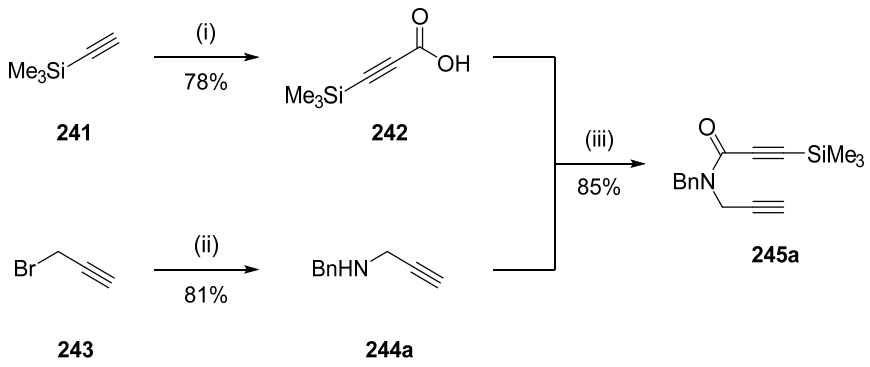
Scheme 19. Proposed synthetic route to highly-substituted isoindolinones.

It was identified that a key challenge of the above approach was controlling the regioselectivity of the cyclization.[137] In order to address this, a trimethylsilyl group was selected as a potential regiodirecting group (**Scheme 19**).[136a] Another important challenge to address was finding safe and sustainable reaction conditions for the alkyne cyclotrimerization. In particular, the DCE solvent used by Yamamoto *et al*. was something that had to be avoided. [137] Having developed optimal cyclization conditions, it would then be necessary to prepare different isoindolinones, by exploring then substrate scope and manipulating the cyclization products. Finally, it would also be interesting to cleave the lactam of isoindolinone **240** to access monocyclic benzene derivatives. Such a "temporary tether" strategy has not been widely reported for [2+2+2]-cycloaddition reactions.[113b, 136e, 136h]

2.2. Results and Discussion

2.2.1. Starting Material Synthesis

Initial efforts focused on the synthesis of amide-tethered diyne **245a** *via* the coupling of carboxylic acid **242** and amine **244a** (**Scheme 20**). Firstly, acid **242** was synthesized in 78% isolated yield by carboxylation of ethynyltrimethylsilane **241** according to the modified procedure of Fleming *et al*. [139] Amine **244a** was formed in 81% isolated yield from propargyl bromide, using 6.0 eq. of benzylamine, as previously reported by Burton and Hess.[140] Using only 3.0 eq. of benzylamine resulted in a 48% yield of amine **244a** due to significant over-alkylation. The coupling of carboxylic acid **242** and amine **244a** in CH_2Cl_2 *via* the corresponding acid chloride gave diyne **245a** in 67% isolated yield. Substituting CH_2Cl_2 with 2-MeTHF, a solvent noted for its sustainable properties,[23] resulted in an improved 85% isolated yield of diyne **245a**. Diyne **245a** was found to be sensitive to desilylation on silica, so rapid purification by flash column chromatography was essential to attain a good yield.

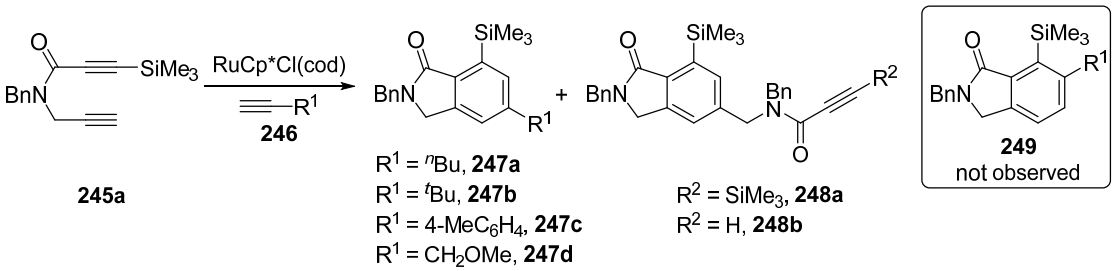


Scheme 20. Starting material synthesis. Reagents and conditions: (i) EtMgBr, then $CO_{2(s)}$; (ii) benzylamine; (iii) oxalyl chloride, DMF, 2-MeTHF then amine **244a**, 2.5 eq. NEt_3, 2-MeTHF.

2.2.3. Preliminary Cyclizations

At the start of this study, the cyclotrimerization of diyne **245a** with a selection of monoynes was briefly investigated. Following Yamamoto's reported work on alkyne cyclotrimerizations, RuCp*Cl(cod) was chosen as a catalyst.[137] A significant disadvantage of Yamamoto's cyclotrimerization protocol is the use of 1,2-dichloroethane (DCE) as solvent, which is potentially detrimental to human health and is generally avoided within industry. Consequently DCE was not used in the preliminary investigations and cyclopentyl methyl ether (CPME) was used as an alternative solvent because of its more environmentally sustainable properties.[23] The results of this study are summarized in **Table 3**.

Table 3. Synthesis of substituted isoindolinones using preliminary cyclization conditions.[a]



Entry	R^1	Time/h	Isolated yield **247**/%	Isolated yield **248**/%	**247**:**248**[b]
1	^{n}Bu	0.5	61	16	2:1
2	^{t}Bu	0.5	22	43	1:3
3	4-MeC_6H_4	1.75[c]	42	10	2:1
4	CH_2OMe	16	47	28	2:1

[a] A solution of 10 mol% RuCp*Cl(cod) and 4.0 eq. monoyne **246** in CPME was added dropwise over 15 minutes to a stirring solution of diyne **245a** in CPME at RT. [b] As determined from a ^{1}H NMR spectrum of the crude product. [c] A co-spot prevented accurate determination of the reaction time by TLC.

Treating diyne **245a** with 4.0 eq. 1-hexyne **246a** and 10 mol% RuCp*Cl(cod) gave isoindolinone **247a**, with complete conversion of diyne **245a** after 30 minutes (**Table 3**, Entry 1). The cyclization was highly regioselective, with no evidence of regioisomer **249** observed in the ^{1}H NMR spectrum of the crude product. However, the ^{1}H NMR spectrum of the crude product indicated the presence of a second isoindolinone **248a**, formed from the homo-coupling of diyne **245a.** Target isoindolinone **247a** was readily separated by flash column chromatography and was isolated in 61% yield. However, homo-coupled product **248a** underwent desilylation on silica gel to give isoindolinone **248b** in 16% yield.

Under the same conditions diyne **245a** readily cyclized with *tert*-butyl acetylene **246b** and 4-ethynyltoluene **246c** to give isoindolinones **247b** and **247c** respectively (**Table 3**, Entries 2 and 3). However, the cyclization with *tert*-butyl acetylene **246b** resulted in significant homo-coupling, with the desired isoindolinone **247b** isolated in only 22% yield. Methyl propargyl ether **246d** also cyclized with diyne **245a** (Entry 4), with isoindolinone **247d** isolated in 47% yield.

Isoindolinones **247a**, **247b** and **247d** and homo-coupled isoindolinones **248a** and **248b** were found to decompose when dissolved in $CDCl_3$. These compounds were stable in DMSO, so from this point onwards DMSO-d_6 was used as a solvent for the acquisition of NMR data for all isoindolinone products.

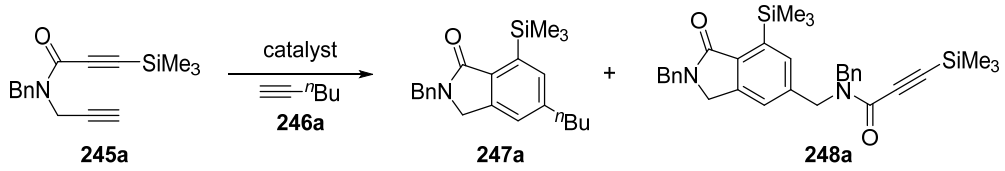
2.2.4. Cyclization Optimization

The results of the preliminary cyclizations were promising, giving reasonable yields in a sustainable solvent under mild reaction conditions. In general the target isoindolinone was formed preferentially over the homo-coupled product. However, there was still significant room for improvement, especially in avoiding the high catalytic loading of RuCp*Cl(cod) and minimizing homo-coupling. To this end a range of reaction conditions were screened.

The reaction chosen to be optimized was the cyclotrimerization of amide-tethered diyne **245a** and 1-hexyne **246a** (**Table 4**). For the purpose of this optimization, all reactions were carried out over 16 h under an argon atmosphere and the unpurified product was analyzed by ^{1}H NMR spectroscopy. For simplicity, the 15 minute dropwise addition of a solution of 1-hexyne **246a** and catalyst to a solution of diyne **245a** was avoided. Instead

a solution of diyne **245a** was added dropwise to a stirring solution of monoyne **246a** and catalyst over 1 minute (unless stated otherwise).

Table 4. Optimization of the cyclotrimerization of diyne 245a and monoyne 246a.



Entry	Solvent	Eq. **246a**	Catalyst [loading/ mol%]	Conversion **245a**[a]/%	**247a:248a**[a]
1	PhMe[b]	4.0	$Rh(PPh_3)_3Cl$ [10]	<5	-
2	PhMe[b]	4.0	$Co_2(CO)_8$ [10]	<5	-
3	DCE[b]	4.0	RuCp*Cl(cod) [1]	5	-
4	CH_2Cl_2[b]	4.0	Grubbs I [5]	5	-
5	neat[c]	4.0	RuCp*Cl(cod) [1]	50	3:2
6	neat[c]	4.0	RuCp*Cl(cod) [3]	100	3:1
7	CPME	4.0	RuCp*Cl(cod) [3]	100	5:1
8	CPME	4.0	RuCp*Cl(cod) [1]	60	4:1
9	CPME	2.0	RuCp*Cl(cod) [3]	100	2:1
10[d]	CPME	4.0	RuCp*Cl(cod) [3]	100	8:1
11[d]	**CPME**	**2.0**	**RuCp*Cl(cod) [3]**	**100**	**9:1**
12[d]	CPME	1.1	RuCp*Cl(cod) [3]	100	2.5:1
13[d]	MTBE	2.0	RuCp*Cl(cod) [3]	100	5:1
14[d]	2-MeTHF	2.0	RuCp*Cl(cod) [3]	90	5:1
15[d]	CPME/10% water	2.0	RuCp*Cl(cod) [3]	70	3:1
16	water	4.0	RuCp*Cl(cod) [3]	30	3:1

[a] Determined from the ^{1}H NMR spectrum of the crude product. [b] Solvent dried over activated 4 Å molecular sieves and degassed. [c] RuCp*Cl(cod) was added to the reaction mixture at 0 °C, which was then allowed to reach RT. [d] Diyne **245a** in CPME was added dropwise over 3 h to a stirring solution of monoyne **246a** and RuCp*Cl(cod).

Initially four different cyclotrimerization procedures reported in the literature were screened for the reaction of diyne **245a** with 1-hexyne **246a** (**Table 4**, Entries 1–4). Neither $RhCl(PPh_3)_3$[141] nor $Co_2(CO)_8$[142] were effective at catalyzing the reaction, with no measurable formation of isoindolinone **247a** (Entries 1 and 2). Using 5 mol% of Grubbs' I in anhydrous, degassed CH_2Cl_2 did generate the desired isoindolinone **247a**, but with only 5% conversion of the diyne **245a** (Entry 3).[143] Use of 1 mol% RuCp*Cl(cod) in anhydrous, degassed DCE also gave isoindolinone **247a**, again with 5% conversion (Entry 4).[137]

Given the poor conversion observed in Entry 4, alternatives to DCE as solvent were considered. When the reaction was conducted without any solvent a significant increase

in conversion of diyne **245a** was observed (**Table 4**, Entry 5). With the higher conversion it was also possible to identify homo-coupled product **248a** in the crude reaction mixture, with **247a** and **248a** formed in the ratio 3:2. Using 3 mol% of RuCp*Cl(cod) resulted in the complete consumption of diyne **245a** within 16 h, with an improved selectivity for isoindolinone **247a** over homo-coupled product **248a** (Entry 6, **247a**:**248a** = 5:1).

Using cyclopentyl methyl ether (CPME) as a solvent gave promising results in the preliminary cyclizations (**Section 2.2.3.**), so it was trialled as a solvent in the optimization study. As shown in Entries 7 and 8 of **Table 4**, the reaction proceeded in CPME and 3 mol% RuCp*Cl(cod) was sufficient to ensure 100% conversion of **245a** within 16 h. In addition, the formation of homo-coupled product **248a** was lower that was observed for the neat reactions. However, reducing the excess of monoyne **246a** resulted in a significant increase in homo-coupling (Entry 9). It is important to note that, unlike previously reported methods for alkyne cyclotrimerizations, it was not necessary to dry or degas the solvent. This was important for both minimizing waste and improving the practicality of the reaction.

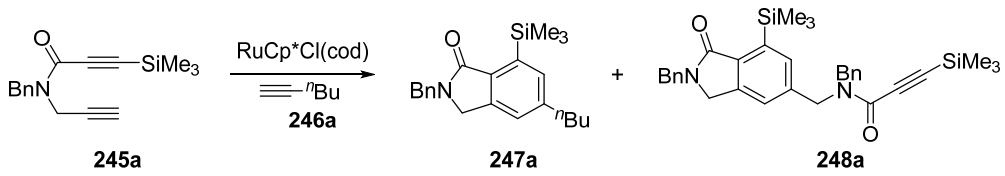
In an attempt to minimize formation of the homo-coupled product **248a**, a 3 h dropwise addition of the diyne was considered.[111] As shown in Entry 10 of **Table 4**, a 3 h dropwise addition resulted in reduced homo-coupling with no decrease in the conversion of diyne **245a**. The 3 h addition also allowed the excess of monoyne **246a** to be reduced from 4.0 eq. to 2.0 eq. with no increase in homo-coupling (Entry 11). As shown in Entry 12, using 1.1 eq. of monoyne **246a** resulted in a significant increase in homo-coupling, but target isoindolinone **247a** was still formed as the major product.

Alternative solvents to CPME were also considered. It was found that methyl *tert*-butyl ether (MTBE) and 2-MeTHF were both effective solvents for the cyclization (**Table 4**, Entries 13 and 14) but neither offered an improvement on CPME. The reaction was also found to be effective when CPME was used in combination with 10% water as a co-solvent (Entry 15), albeit with reduced conversion and increased homo-coupling. In fact, isoindolinone **247a** was formed where water was exclusively used as solvent, with 30% conversion of diyne **245a** (Entry 16). This is significant as it could enable the extension of the reaction to aqueous conditions for reactions involving water-soluble substrates.

The conditions described in Entry 11 of **Table 4** were taken to be the optimized cyclization conditions, as they maximized conversion while minimizing catalyst loading

and homo-coupling. However, before developing the reaction scope, two areas were investigated further. It was found that the reaction benefited from prolonged dropwise addition of diyne to a solution of monoyne and catalyst, but the effect of the addition time had not been fully explored. Secondly, all the experiments in **Table 4** were conducted under an atmosphere of argon. If the reaction could be performed under an atmosphere of air with no detrimental outcome then this would allow for a more practical reaction. The results of the investigation are shown in **Table 5**.

Table 5. Further investigation of the cyclotrimerization of diyne 245a and 1-hexyne 246a.[a]



245a **247a** **248a**

Entry	Addition time/h	Conversion **245a**[b]/%	**247a:248a**[b]
1	6	100	10:1
2	3	100	9:1
3	1	100	4:1
4[c]	3	80	3:1
5[c]	1	100	4:1

[a] Diyne **245a** in CPME was added dropwise over the designated time period to a stirring solution of 2.0 eq.1-hexyne **246a** and 3 mol% RuCp*Cl(cod) in CPME. The reaction was stirred for a total of 16 h. [b] Determined from the ^{1}H NMR spectrum of the crude product. [c] The reaction was conducted under air rather than argon.

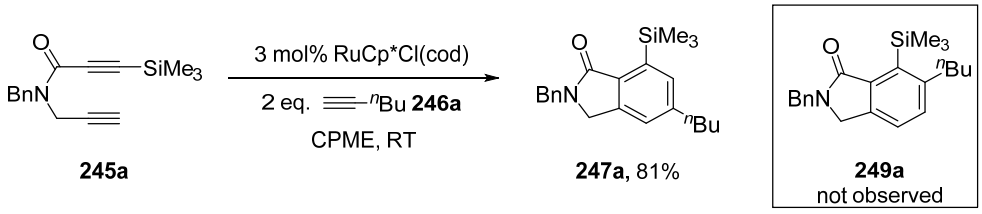
As shown in Entries 1 and 2 of **Table 5**, adding a solution of the diyne dropwise to a solution of monoyne and catalyst over 6 h rather than 3 h did not significantly reduce formation of diyne homo-coupling product **248a**. However, a shorter addition time resulted in increased diyne homo-coupling (Entry 3). This suggested that a 3 h dropwise addition was optimal.

Conducting the reaction with a 3 h dropwise addition under an atmosphere of air resulted in both reduced conversion of diyne **245a** and an increase in diyne homo-coupling (**Table 5**, Entries 4 and 2). However, when the reaction was conducted under air using a 1 h dropwise addition the result was analogous to the corresponding reaction under argon (Entries 5 and 3). This suggested that the reaction was only sensitive to oxygen when the reaction was prolonged by a long (>1 h) dropwise addition.

The optimized reaction conditions are given below. These reaction conditions were used to convert diyne **245a** (70 mg) and 1-hexyne **246a** into isoindolinone **247a** with an 81%

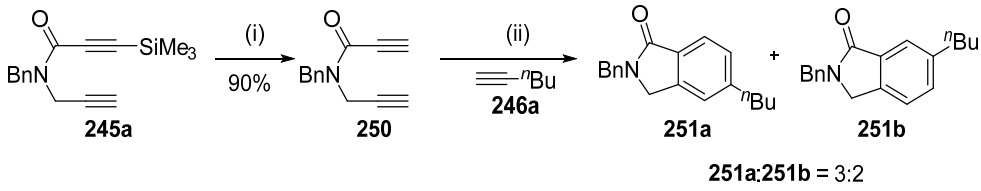
isolated yield (**Scheme 21**). This represented a significant improvement in terms of isolated yield compared to the preliminary cyclization conditions. In addition, both catalytic loading and the excess of monoyne had been reduced. Importantly the reaction was highly regioselective; regioisomer **249a** was not observed at any point in this study. This reaction was also scaled up to use 500 mg of **245a** and isoindolinone **247a** was isolated in 66% yield.

*A solution of diyne in CPME was added dropwise over 3 h to a stirring solution of 2.0 eq. monoyne and 3 mol% RuCp*Cl(cod) in CPME at RT under an atmosphere of argon. The reaction was stirred at RT for a total of 16 h. CPME was used without degassing or drying.*



Scheme 21. Optimized cyclization of diyne 245a and 1-hexyne 246a.

To confirm that the trimethylsilyl group was responsible for controlling the regioselectivity of the alkyne cyclotrimerization rather than the reaction conditions, diyne **250** was treated with 1-hexyne **246a** and RuCp*Cl(cod) under the optimized conditions described. As shown in **Scheme 22**, the regioselectivity of this cyclization was poor. This suggested that, as expected, the trimethylsilyl group of diyne **245a** was acting as an effective regiodirecting group. The regioselectivity of this cyclization was comparable with the regioselectivity of the same reaction reported under Yamamoto's conditions (**Section 2.1.4., Table 2**, Entry 1).[137]



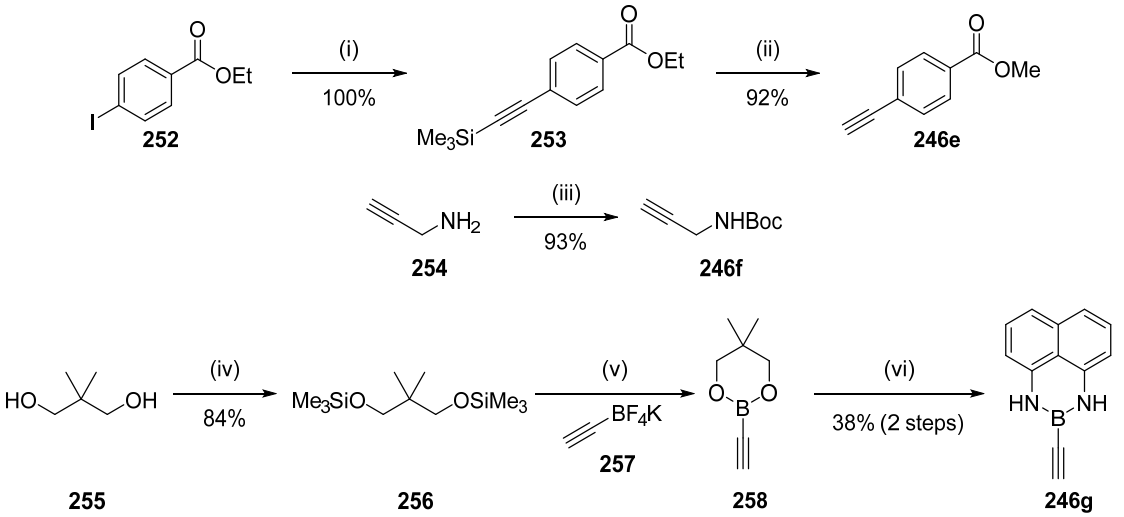
Scheme 22. Cyclization of diyne 250 and 1-hexyne 246a under optimized conditions. Reagents and conditions: (i) K_2CO_3, MeOH; (ii) 3 mol% RuCp*Cl(cod), CPME, 16 h, RT.

2.2.5. Monoyne Scope

Having established optimized reaction conditions for the cyclotrimerization of amide-tethered diyne **245a** with 1-hexyne **246a** it was then important to explore the general applicability of the reaction by considering different monoynes.

Monoyne Synthesis

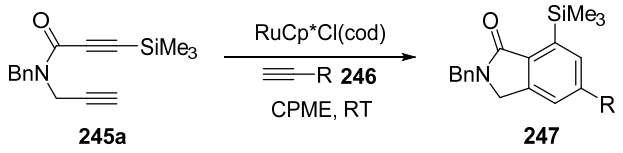
While the majority of the monoynes used in this section were sourced commercially, three monoynes were prepared in the laboratory (**Scheme 23**). Benzoate alkyne **246e** was synthesized in 92% isolated yield over two steps *via* a Sonogashira coupling of aryl iodide **252** with ethynyltrimethylsilane, followed by desilylation and transesterification using K_2CO_3 in MeOH.[144] Carbamate **246f** was prepared from propargylamine **254** and Boc_2O in 93% isolated yield.[145] Alkynyl boramide **246h** was prepared over three steps from diol **255**. Disilyl ether **256** was prepared from diol **255**,[146] which was then treated with potassium ethynyl trifluoroborate **257** and Me_3SiCl to give aryl borate ester **258**. The crude aryl borate ester **258** was then treated with naphthalene-1,8-diamine to yield boramide **246g**, which was purified by flash column chromatography without special precautions.



Scheme 23. Monoyne synthesis. Reagents and conditions: (i) $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, $Me_3SiC{\equiv}CH$; (ii) K_2CO_3, MeOH; (iii) $(Boc)_2O$; (iv) $NH(SiMe_3)_2$, Me_3SiCl; (v) Me_3SiCl; (vi) naphthalene-1,8-diamine.

Cyclizations with Different Monoynes

For the purpose of this study a series of monoynes were treated with *N*-Bn diyne **245a** using the optimized reaction conditions (**Scheme 24**). Reactions that did not reach completion within 16 h were left for a total of 24 h. If this failed to result in 100% conversion of diyne **245a** then catalyst loading was increased.

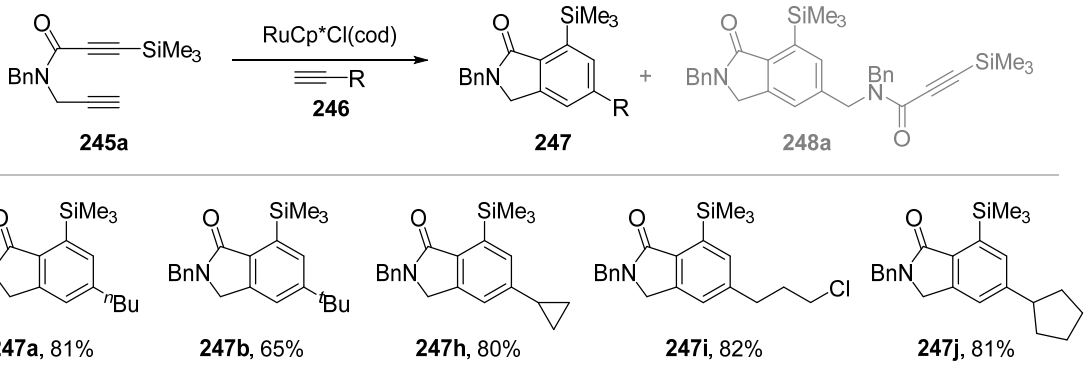


Scheme 24. Cyclization of diyne 245a with a selection of monoynes.

Aliphatic Monoynes

All the aliphatic monoynes explored in **Table 6** cyclized with amide-tethered diyne **245a** to give the corresponding isoindolinones **247** in 65–83% isolated yield without modification of the optimized reaction conditions. All five reactions were conducted in duplicate to demonstrate the reproducibility of the reaction. All of these cyclizations occurred with a low level of homo-coupling, except for the reaction to form isoindolinone **247b** from *tert*-butylacetylene, where **247b**:**248a** = 2:1 (Entries 3 and 4).

Table 6. Cyclization of diyne 245a with aliphatic monoynes.[a]



Entry	R	Time/ h	[Ru]/ mol %	**247**	Conversion of **245a**/%[a]	Isolated yield **247**/%	**247: 248a**[b]
1	^{n}Bu	16	3	**247a**	100	81	9:1
2	^{n}Bu	16	3	**247a**	100	82	8:1
3	^{t}Bu	16	3	**247b**	100	65	2:1
4	^{t}Bu	16	3	**247b**	100	65	2:1
5	^{c}Pr	16	3	**247h**	100	78	9:1
6	^{c}Pr	16	3	**247h**	100	81	11:1
7	$CH_2CH_2CH_2Cl$	16	3	**247i**	100	83	9:1
8	$CH_2CH_2CH_2Cl$	16	3	**247i**	100	81	7:1
9	$CH(CH_2CH_2)_2$	16	3	**247j**	100	80	6:1
10	$CH(CH_2CH_2)_2$	16	3	**247j**	100	81	6:1

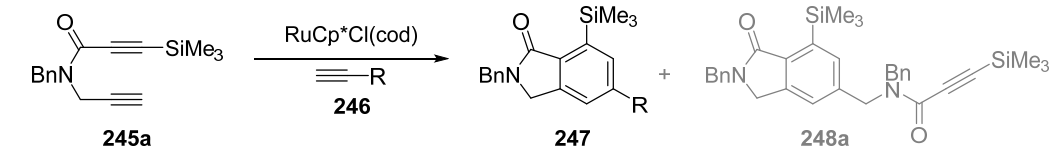
[a] Reagents and conditions: RuCp*Cl(cod), CPME, RT. The yields quoted with the structures are averaged over two experiments. [b] Determined from the ^{1}H NMR spectrum of the crude product by the integration of peaks relating to compounds **245a**, **247** and **248a.**

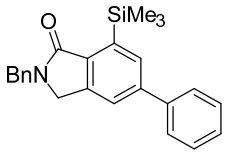
Aromatic Monoynes

The reaction of a diyne **245a** with a series of substituted phenyl acetylenes was explored, with the results summarized in **Table 7**. The reaction of diyne **245a** with phenylacetylene

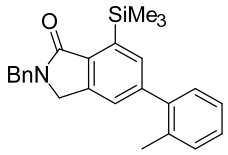
(**Table 7**, Entries 1–3) was slower than the corresponding reaction with 1-hexyne (**Table 6**, Entries 1 and 2) and the reaction required 4 mol% RuCp*Cl(cod) and 24 h to reach completion. Following this isoindolinone **247k** was isolated in 83% yield (**Table 7**, Entry 3). In contrast, the reaction of diyne **245a** with 2-tolylacetylene required only 3 mol% RuCp*Cl(cod) to reach completion within 16 h (Entries 4 and 5) The corresponding isoindolinone **247l** was isolated in 93% yield, with negligible diyne homo-coupling observed in the crude ^{1}H NMR spectrum. It is notable that 4-tolylacetylene behaved like phenylacetylene (Entries 6–8); 4 mol% RuCp*Cl(cod) and a 24 h reaction time resulted in 100% conversion of diyne **245a** and a 83% isolated yield of **257n**.

Table 7. Cyclization of diyne 245a with aromatic monoynes.[a]

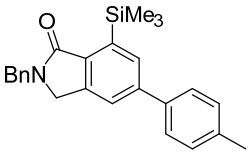




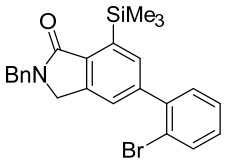
247k, 83%



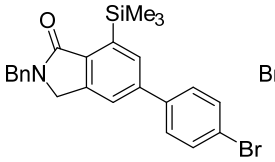
247l, 93%



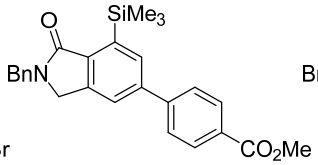
247c, 81%



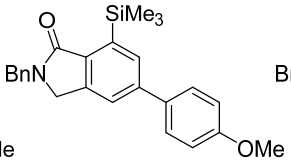
247m, 80%



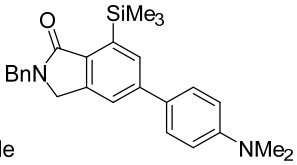
247n, 83%



247e, 79%



247o, 79%



247p, 79%

Entry	R	Time/ h	[Ru]/ mol %	**247**	Conversion **245a**/%[b]	Isolated yield **247**/%	**247: 248a**[b]
1	Ph	16	3	**247k**	90	n.d.	7:1
2	Ph	24	3	**247k**	80	n.d.	5:1
3	Ph	24	4	**247k**	100	83	6:1
4	2-MeC_6H_4	16	3	**247l**	100	n.d.	>10:1
5	2-MeC_6H_4	16	3	**247l**	100	93	>10:1
6	4-MeC_6H_4	16	3	**247c**	80	n.d.	3:1
7	4-MeC_6H_4	24	3	**247c**	90	79	7:1
8	4-MeC_6H_4	24	4	**247c**	100	81	6:1
9	2-BrC_6H_4	16	3	**247m**	100	n.d.	6:1
10	2-BrC_6H_4	16	3	**247m**	100	80	8:1
11	4-BrC_6H_4	24	3	**247n**	100	83	5:1
12	4-BrC_6H_4	24	3	**247n**	100	78	5:1
13	4-$(MeO_2C)C_6H_4$	24	3	**247e**	100	79	5:1
14	4-$(MeO)C_6H_4$	24	4	**247o**	90	n.d.	5:1
15	4-$(MeO)C_6H_4$	24	5	**247o**	100	79	6:1
16	4-$(Me_2N)C_6H_4$	24	6	**247p**	80	n.d.	3:1
17	4-$(Me_2N)C_6H_4$	24	10	**247p**	90	79	7:1

[a] Reagents and conditions: RuCp*Cl(cod), CPME, RT. [b] Determined from the ^{1}H NMR spectrum of the crude product by the integration of peaks relating to compounds **245a**, **247** and **248a**.

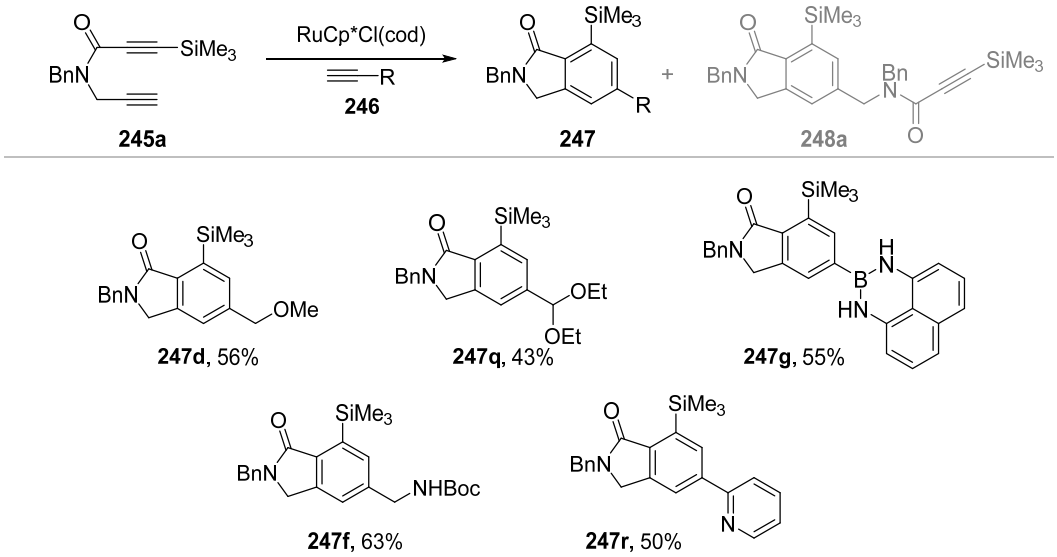
The reaction of diyne **245a** with 2-bromo and 4-bromophenylacetlyne proceeded efficiently using 3 mol% RuCp*Cl(cod) to give isoindolinones **247m** and **247n** in 80% and 83% isolated yield respectively (**Table 7**, Entries 9–12). Using 4-(methoxycarbonyl)phenylacetylene as the monoyne similarly gave the desired isoindolinone **247e** in 79% isolated yield, again with only 3 mol% of the catalyst required (Entry 13). The reaction of diyne **245a** with 4-methoxyphenylacetlyene required a higher

catalyst loading to reach completion (5 mol% RuCp*Cl(cod)), with isoindolinone **247o** isolated in 79% yield (Entries 14 and 15). The reaction of 4-(dimethylamino) phenylacetylene with diyne **245a** required a higher catalyst loading to achieve reasonable conversion of diyne **245a** (Entries 16 and 17). Using 10 mol% RuCp*Cl(cod) resulted in 90% conversion of diyne **245a**, with isoindolinone **247p** isolated in 79% yield.

Other Monoynes of Interest

Ether **247d** and acetal **247q** were formed using 3 mol% RuCp*Cl(cod), but in low isolated yields (56% and 43% respectively) owing to significant diyne homo-coupling (**Table 8**, Entries 1–4). The methodology was extended to form aryl boramide **247g** using 5 mol% RuCp*Cl(cod) in 55% isolated yield (Entries 5 and 6). Gandon *et al*.[129b] have reported that aryl boramides can be transformed to the analogous aryl boronic acid under strong acidic conditions, which can then be used for cross coupling. The reaction to form isoindolinone **247e** occurred with relatively high homo-coupling of diyne **245a**, but isoindolinone **247e** was isolated in 63% yield (Entries 7 and 8). The corresponding reaction of 2-ethynylpyridine **246r** was comparatively slow and required 20 mol% RuCp*Cl(cod) to achieve 80% conversion of diyne **245a** (Entries 9–11). The reaction also occurred with significant diyne homo-coupling and isoindolinone **247r** was isolated in 50% yield.

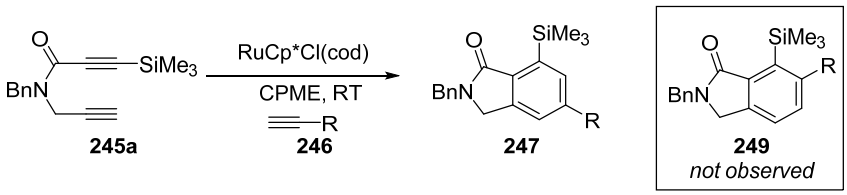
Table 8. Cyclization of diyne 245a with other monoynes of interest.



Entry	R	Time/ h	[Ru]/ mol %	**247**	Conversion of **245a**/%[b]	Yield **247**/%	**247: 248a**[b]
1	CH_2OMe	16	3	**247d**	100	56	3:2
2	CH_2OMe	16	3	**247d**	100	n.d.	3:2
3	$CH(OEt)_2$	16	3	**247q**	90	29	0.7:1
4	$CH(OEt)_2$	24	3	**247q**	100	43	0.8:1
5	$B(C_{10}H_8N_2)$	16	3	**247g**	70	n.d.	3:1
6	$B(C_{10}H_8N_2)$	24	5	**247g**	100	56	3:1
7	CH_2NHBoc	16	3	**247f**	80	n.d.	3:1
8	CH_2NHBoc	24	5	**247f**	100	63	2:1
9	pyridin-2-yl	24	3	**247r**	15	n.d.	3:2
10	pyridin-2-yl	24	10	**247r**	60	n.d.	3:2
11	pyridin-2-yl	24	20	**247r**	80	50	2:1

[a] Reagents and conditions: RuCp*Cl(cod), CPME, RT. [b] Determined from the ^{1}H NMR spectrum of the crude product by the integration of peaks relating to compounds **245a**, **247** and **248a.**

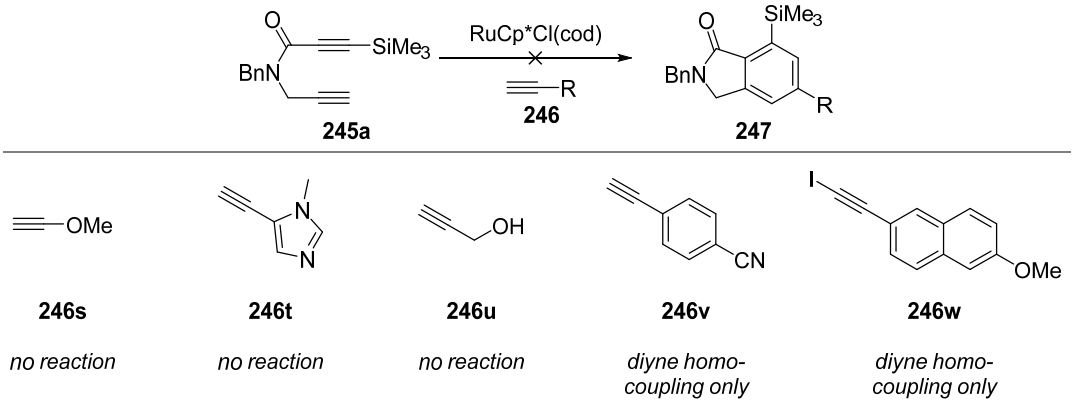
It is important to note that for all of the cyclizations in this section (**Table 6**, **Table 7** and **Table 8**) that the target isoindolinone was formed with excellent regioselectivity (**Scheme 25**). Regioisomer **249** was not observed in the crude ^{1}H NMR spectra of any reaction in the above study. This suggested that the trimethylsilyl directing group of diyne **245a** could effectively control regioselectivity for the reaction of **245a** with a wide variety of monoynes under the optimized conditions.



Scheme 25. Highly regioselective cyclizations.

Failed Cyclizations

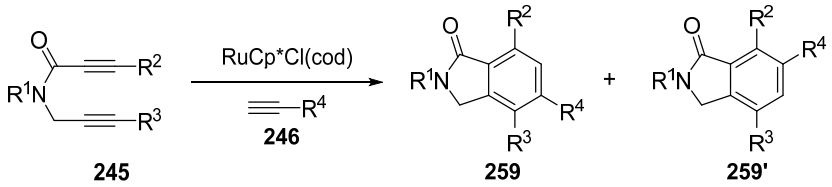
The monoynes depicted in **Scheme 26** failed to cyclize with diyne **245a** under the optimized reaction conditions to form an isoindolinone product. No reaction was observed when alkynes **246s** and **246t** were subjected to the cyclization conditions. The fact that not even homo-coupling was observed suggested that in both cases the monoyne deactivated the catalyst. The addition of propargyl alcohol **246u** to a solution of RuCp*Cl(cod) resulted in the formation of a precipitate and again no cyclization occurred. Treating diyne **245a** with benzonitrile **246v** only resulted in the limited diyne homo-coupling. Diyne **245a** was also treated with internal iodoalkyne **246w** but again the only observed reaction was the homo-coupling of diyne **245a**.



Scheme 26. Monoynes that failed to cyclize with diyne 245a under the optimized cyclization conditions.

2.2.6. Diyne Scope

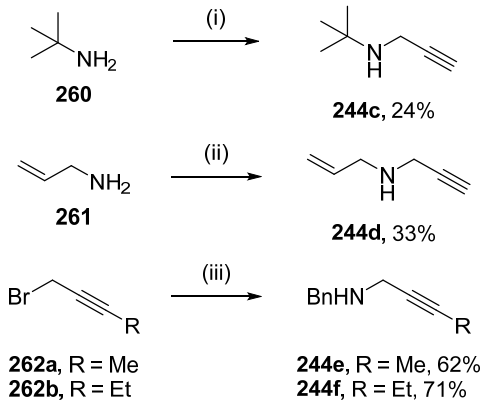
In addition to demonstrating reaction scope with respect to monoyne, it was important to demonstrate the versatility of the reaction with different amide-tethered diynes (**Scheme 27**). The reaction was explored using a variety of amide-tethered diynes with different substituents at the *N*-position (R^1) and different alkynyl substituents (R^2 and R^3).



Scheme 27. Probing the diyne scope of the optimized reaction.

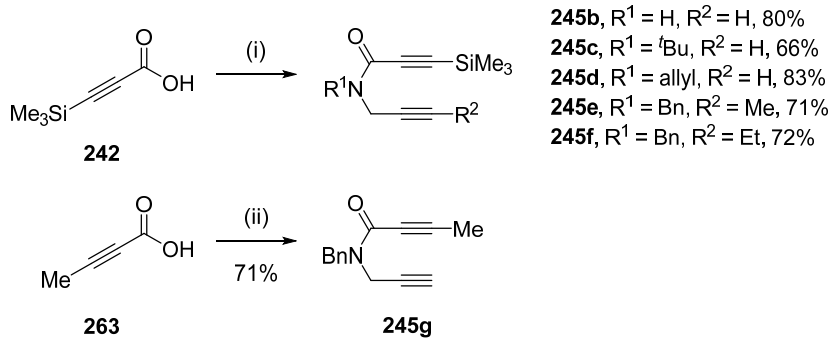
Diyne Synthesis

In order to synthesize a range of new diynes it was necessary to make four different propargylic amines (**Scheme 28**). The general approach to synthesize this group of compounds was to treat the corresponding primary amine was a propargyl halide. Amines **244c**[147] and **244d**[148] were both isolated in low yields following vacuum distillation. Amines **244e** and **244f** were isolated in 62% and 71% yields respectively following purification by flash column chromatography.[140]



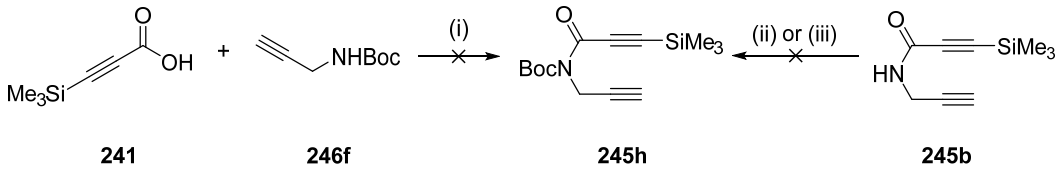
Scheme 28. Amine synthesis. Reagents and conditions: (i) propargyl bromide; (ii) propargyl chloride; (iii) benzylamine.

With the propargylic amines in hand, five amide-tethered diynes were prepared in 66–83% isolated yield using the coupling procedure developed for *N*-Bn diyne **245a** (**Scheme 29**). This method was unsuited to the synthesis of diyne **245g**, with little formation of the desired product. However, diyne **245g** was prepared in 71% isolated yield using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) as coupling reagent.[137]



Scheme 29. Diyne synthesis. Reagents and conditions: (i) oxalyl chloride, DMF, 2-MeTHF then amine **244**, NEt_3, 2-MeTHF; (ii) $BnHNCH_2C{\equiv}CH$ **244a**¸ EDC, DMAP, CH_2Cl_2.

In addition to the amide-tethered diynes above, *N*-Boc diyne **245h** was identified as an interesting substrate for an alkyne cyclotrimerization. However, three different strategies failed to yield *N*-Boc diyne **245h** (**Scheme 30**). Conversion of carboxylic acid **241** to the corresponding acid chloride followed by treatment with carbamate **246f** failed to yield the desired diyne. *N*-H diyne **245b** proved to be unstable in the presence of Boc_2O and DMAP in MeCN, with neither starting material nor product recovered from the reaction. Similarly, treating diyne **245b** with Boc_2O and NEt_3 in CH_2Cl_2 was unsuccessful.



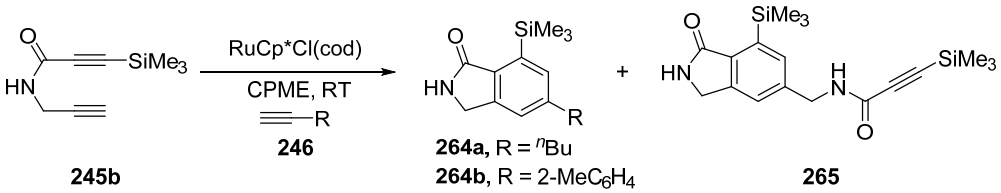
Scheme 30. Failed attempts at the synthesis of *N*-Boc diyne 245h. Reagents and conditions: (i) oxalyl chloride, DMF, 2-MeTHF then carbamate **246f**, NEt_3, 2-MeTHF; (ii) $(Boc)_2O$, DMAP, MeCN; (iii) $(Boc)_2O$, NEt_3, CH_2Cl_2.

Cyclizations Involving Different *N*-Substitution of the Diyne

N-H Diyne

Under the optimized reaction conditions *N*-H diyne **245b** cyclized with 1-hexyne **246a** to form *N*-H isoindolinone **264a**, but with only 50% conversion of diyne **245b** and significant formation of homo-coupled product **265** (**Table 9**, Entry 1). A longer reaction time increased the conversion of **245b**; but the reaction only reached 75% conversion after 5 days (Entry 2). Increasing the reaction temperature to 50 °C had no impact on either the conversion of **245b** or the level of homo-coupling (Entry 3). The most effective method for maximizing conversion and selectivity was to use 10 mol% RuCp*Cl(cod) and a 24 h reaction time, which gave a 51% isolated yield of isoindolinone **264a** (Entry 4). Under the same conditions 2-ethynyltoluene cyclized with *N*-H diyne **245b** with a 62% isolated yield of isoindolinone **254b** and 90% conversion of diyne **245b** (Entry 5).

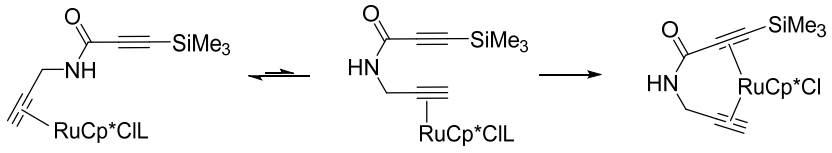
Table 9. Cyclization of *N*-H diyne 245b with monoynes.



Entry	R	[Ru]/ mol%	Time	**264**	Conversion **245b**/%[a]	Isolated yield **264**/%	**264:265**[a]
1	^{n}Bu	3	16 h	**264a**	50	-	3:2
2	^{n}Bu	3	5 days	**264a**	75	-	3:2
3[b]	^{n}Bu	3	16 h	**264a**	50	-	3:2
4	^{n}Bu	10	24 h	**264a**	90	51	2:1
5	2-MeC$_6$H$_4$	10	24 h	**264b**	90	62	7:1

[a] Determined from the ^{1}H NMR spectrum of the crude product. [b] Reaction conducted at 50 °C.

The observation that *N*-H diyne **245b** was slower to cyclize with 1-hexyne that *N*-Bn diyne **245a** was expected when the mechanism was considered (**Scheme 31**). The mechanism for RuCp*Cl(cod)-catalyzed alkyne cyclotrimerizations is believed to proceed through a bidentate complex of the diyne with RuCp*Cl (complex **266c**). This is formed from monodentate complex **266b**, where the two alkyne units are *syn* with respect to the amide bond. This, however, will be the minor rotamer in solution. It is sterically more favorable for the diyne to exist in an *anti*-conformation (complex **266a**), where the propargyl group is pointing away from the internal alkyne, and this would retard the cyclization. *N*-Bn diyne **245a** would also exist in an analogous rotameric equilibrium when in solution, but the sterically bulky benzyl substituent can shift the equilibrium further in favor of the reactive *syn*-conformation.



anti-rotamer, **266a** *syn*-rotamer, **266b** **266c**

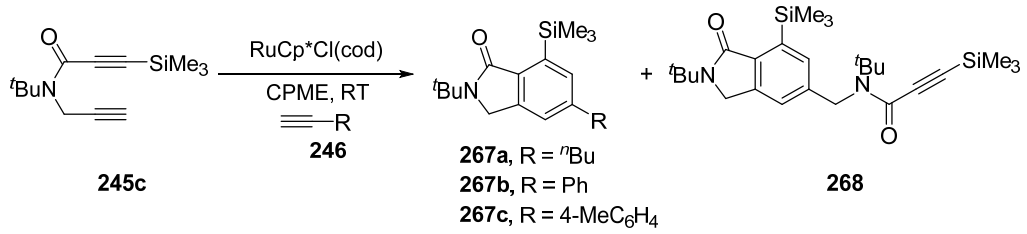
Scheme 31. Equilibrium between rotameric intermediates.

N-^{t}Bu Diyne

The *N*-^{t}Bu diyne **245c** cyclized with 1-hexyne **246a** under the optimized reaction conditions to give isoindolinone **267a** in 84% yield and with little formation of homo-coupled product **268** (**Table 10**, Entry 1). The reaction of diyne **245c** with

phenylacetylene was slower, requiring 24 h and 4 mol% RuCp*Cl(cod) to reach completion (Entry 2). However, isoindolinone **267b** was formed in 89% yield and with almost no homo-coupled product **268**. Finally, 2-ethynyltoluene also cyclized with diyne **245c** to give isoindolinone **267c** in 94% yield and very little homo-coupling was observed (Entry 3).

Table 10. Cyclization of *N*-^{t}Bu diyne 245c with monoynes.

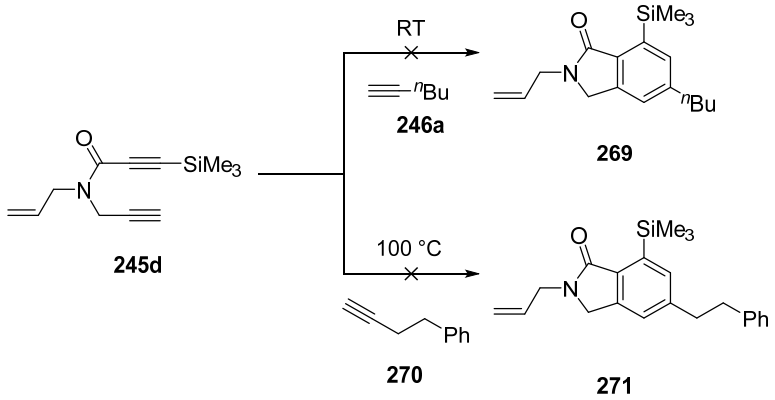


Entry	R	[Ru]/ mol%	Time/ h	**267**	Isolated yield **267**/%	**267:268**[a]
1	^{n}Bu	3	16	**267a**	84	10:1
2	Ph	4	24	**267b**	89	>10:1
3	2-MeC$_6$H$_4$	3	16	**267c**	94	>10:1

[a] Determined from the ^{1}H NMR spectrum of the crude product.

N-Allyl Diyne

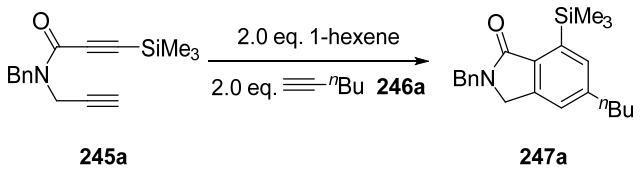
Subjecting *N*-allyl diyne **245d** to the optimized reaction conditions with 1-hexyne **246a** resulted in no reaction and the recovery of starting material (**Scheme 32**). Cyclization was also not observed when the reaction was conducted at 100 °C in a sealed tube with but-3-yn-1-ylbenzene **270** (chosen for its high boiling point).



Scheme 32. Failed cyclizations involving *N*-allyl diyne 245d. Reagents and conditions: 3 mol% RuCp*Cl(cod), CPME.

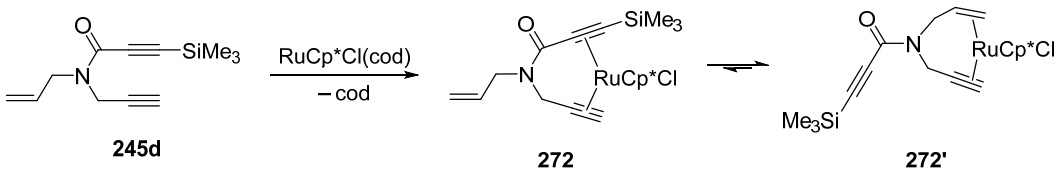
A possible conclusion from the failure to cyclize *N*-allyl diyne **245d** is that the optimized reaction conditions are ineffective in the presence of a terminal alkene. To test this hypothesis, *N*-Bn diyne **245a** was treated with 1-hexyne **246a** under the optimized

conditions in the presence of 2.0 eq. of 1-hexene (**Scheme 33**). The alkene had no significant impact on the reaction, with only a slight drop in conversion after 16 h. This suggested that the optimized reaction conditions could tolerate the presence of alkenes in general and that a more subtle effect was hampering the reaction of diyne **245d** with monoynes.



Scheme 33. Reaction of diyne 245a and 1-hexyne 246a in the presence of 1-hexene. Reagents and conditions: 3 mol% RuCp*Cl(cod), CPME, 16 h, RT.

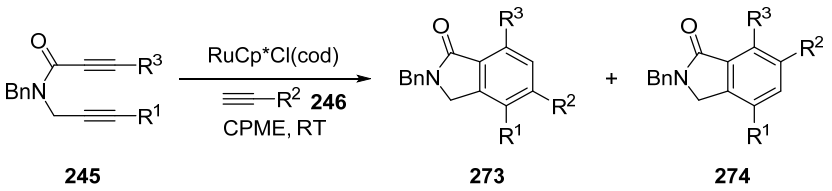
A potential explanation is depicted in **Scheme 34**. The key step in the cyclization of *N*-allyl diyne **245d** would be the oxidative cyclization of bidentate complex **272**. However, it is possible that the Ru centre complexes preferentially with the pendent alkene rather than the internal alkyne to form complex **272'**. If the catalytic species remained in this unreactive complex **272'** then no reaction could proceed.



Scheme 34. Hypothetical complexation between the catalytic species and *N*-allyl diyne 245d.

Cyclizations Involving Different Alkyne-Substitution of the Diynes

A key strength of this methodology is its regioselectivity; minor regioisomer **274** was not observed in any cyclotrimerization reported to this point. To expand the reaction scope further and probe the question of regioselectivity a number of other cyclizations were examined (**Scheme 35**). Firstly, an extra substituent R^1 was incorporated into the diyne, weakening the diyne's regiochemical bias. Secondly, a diyne where the regiodirecting group R^3 was not $SiMe_3$ was examined, to see whether the high regioselectivity was maintained.

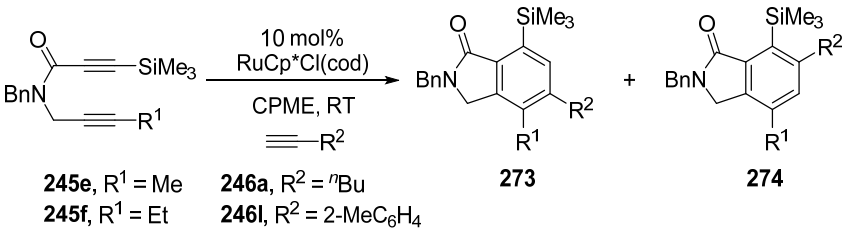


Scheme 35. Investigating the regioselectivity of alkyne cyclotrimerizations.

Internal Diynes

Preliminary cyclizations of diynes **245e** and **245f** with 1-hexyne **246a** indicated that 10 mol% was a suitable level of catalyst loading to ensure complete conversion of the diyne within 24 h. They also showed that the internal diynes were not susceptible to homo-coupling. For this reason, the 3 h dropwise addition of diyne to monoyne and catalyst was omitted for simplicity. Four cyclizations were conducted and the results are given in **Table 11.**

Table 11. Cyclization involving internal diynes.[a]



Entry	Diyne	R^1	R^2	Isolated products	Yield (**273** + **274**)/%	**273:274**[b]
1	**245e**	Me	^{n}Bu	**273a/274a**	69[c]	9:1
2	**245e**	Me	2-MeC_6H_4	**273b**	88[d]	>20:1
3	**245f**	Et	^{n}Bu	**273c/274c**	57[c]	2:1
4	**245f**	Et	2-MeC_6H_4	**273d/274d**	73[c]	5:1

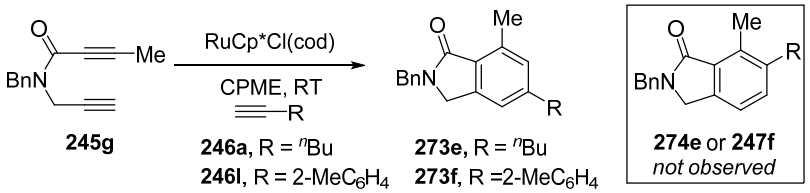
[a] A solution of diyne **245** in CPME was added to a stirring solution of 2.0 eq. monoyne **246** and 10 mol% RuCp*Cl(cod) in CPME over 1 minute. The reaction was stirred at RT for 24 h. Determined from the ^{1}H NMR spectrum of the crude product. [c] Isolated yield. [d] Estimated from the ^{1}H NMR spectrum of the crude product by integration of peaks corresponding to isoindolinone **245e** and those of impurities.

The cyclization of methyl-substituted diyne **245e** with 1-hexyne **246a** gave a 9:1 mixture of regioisomers **273a** and **274a** in 69% combined isolated yield (**Table 11**, Entry 1). The reaction of diyne **245e** and 2-ethynyltoluene **246l** was more regioselective, with no evidence of isoindolinone **274b** in the crude ^{1}H NMR spectrum (Entry 2). Unfortunately, it was not possible to purify isoindolinone **273b** as it was sensitive to degradation on silica gel to give an unidentified mixture of impurities. Ethyl-substituted diyne **245f** also cyclized with 1-hexyne **246a** and 2-ethynyltoluene **246l**, but with reduced regioselectivity in both instances (Entries 3 and 4).

A Diyne with a Methyl Regiodirecting Group

Using the optimized reaction condition for the cyclization of diyne **245g** and 1-hexyne **246a** gave isoindolinone **273e** in 85% yield as a single regioisomer (**Table 12**, Entry 1). Evidence of limited homo-coupling of **245g** was observed in the ^{1}H NMR spectrum of the crude product but these impurities were not isolated. Reducing the loading of RuCp*Cl(cod) to 1 mol% resulted in a lower conversion of diyne **245g** (Entry 2). Diyne **245g** also cyclized efficiently with 2-ethynyltoluene **246l** to give isoindolinone **273f** as the only product (Entry 3).

Table 12. Cyclization involving diyne 245g.[a]



Entry	R	[Ru]/ mol%	Time/h	Isolated product	Conversion **245g**/ %[b]	Isolate yield **273**/%
1	^{n}Bu	3	16	**273e**	100	85
2	^{n}Bu	1	16	**273e**	40	27
3	2-MeC$_6$H$_4$	3	16	**273f**	100	94

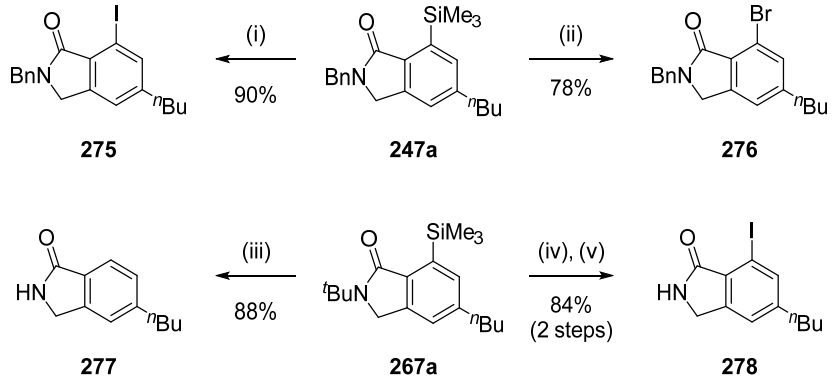
[a] A solution of diyne **245g** in CPME was added to a stirring solution of 2.0 eq. monoyne **246** and RuCp*Cl(cod) in CPME over 3 h. The reaction was stirred at RT for 16 h. Determined from the ^{1}H NMR spectrum of the crude product.

2.2.7. Functional Group Manipulation of Cyclized Products

Transformation of the 2- and 7-Position.

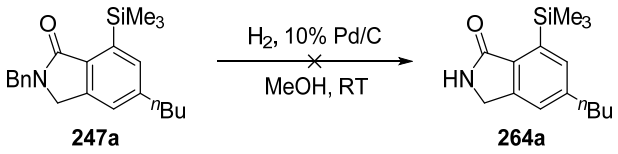
In order to demonstrate the potential use of the developed methodology, functional group manipulation of the cyclotrimerization products was investigated to access novel isoindolinone products. Treatment of isoindolinone **247a** with ICl or Br_2 in CH_2Cl_2 led to aryl iodide **275** and aryl bromide **276** respectively in good yields (**Scheme 36**).[149,150] Replacing the CH_2Cl_2 solvent for the iodination of isoindolinone **247a** with environmentally more benign 2-MeTHF resulted in no reaction. Treatment of *N*-^{t}Bu isoindolinone **267a** with TfOH resulted in a simultaneous deprotection of the lactam and protodesilylation within 30 minutes to give *N*-H isoindolinone **277** in 88% isolated yield.[151] It was not possible to substitute TfOH with TFA; heating **267a** in neat TFA at reflux for 48 h resulted in a complex mixture of products with no evidence of an *N*-H isoindolinone product by ^{1}H NMR spectroscopy. Treatment of **267a** with ICl followed by deprotection with TfOH gave 7-iodo isoindolinone **278** in 84% isolated yield over two

steps. Thus, an *N*-^{t}Bu diyne can be used as an indirect method for the synthesis of *N*-H isoindolinones *via* this acid-mediated deprotection strategy.



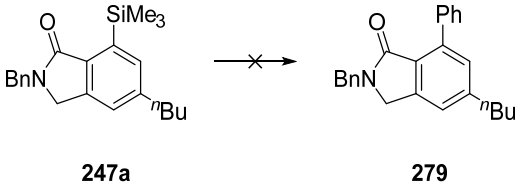
Scheme 36. Functional group manipulation of isoindolinones 247a and 267a. Reagents and conditions: (i) ICl, CH_2Cl_2; (ii) Br_2, CH_2Cl_2; (iii) TfOH; (iv) ICl, CH_2Cl_2; (v) TfOH.

A useful transformation for the *N*-Bn isoindolinone products would be their deprotection to make the corresponding *N*-H isoindolinones. Benzyl deprotection of amides is often carried out *via* a dissolving metal reduction, but such a reaction is unlikely to be selective for the benzyl aromatic ring. Hydrogenation was considered to be more amenable towards the isoindolinone core, but unfortunately resulted in no reaction (**Scheme 37**).[152] Hydrogenation under elevated pressure may be more effective.



Scheme 37. Failed deprotection of *N*-benzyl isoindolinone 247a.

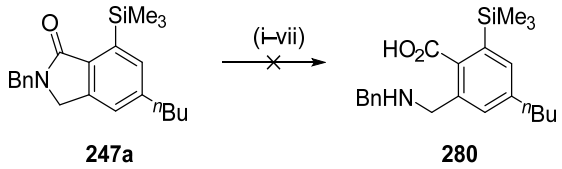
In 2005 Zhao and Snieckus reported a one-pot procedure for the *ipso*-borodesilylation of aryl silanes followed by a Suzuki-Miyaura cross-coupling with aryl halides to access biaryl products.[153] Unfortunately, the application of their protocol to isoindolinone **247a** did not result in any reaction (**Scheme 38**).



Scheme 38. Failed synthesis of biaryl 279 by Snieckus' one-pot cross-coupling procedure.[153] Reagents and conditions: BBr_3, CH_2Cl_2, 2 h 0 °C to RT, then concentrated and treated with PhI, $Pd(PPh_3)_4$, DME, 2.0 M aq. Na_2CO_3, 5 h, reflux.

Lactam Ring-Opening

One of the aims of this project was to cleave the lactam of a cyclotrimerization product, in order to demonstrate that an amide can be used as a temporary tether to access a monocyclic benzene derivative (**Section 2.1.6.**). Initially the hydrolytic cleavage of isoindolinone **247a** was investigated under different reaction conditions (**Scheme 39**). Stirring isoindolinone **247a** in 1.0 M aq. NaOH and either THF, 2-MeTHF or CPME at RT resulted in no reaction. Heating isoindolinone **247a** in 1:1 1.0 M aq. NaOH:CPME at reflux over 3 days similarly resulted in no reaction. Heating isoindolinone **247a** in 10:1 1.0 M aq. NaOH:MeOH at reflux for 3 days was just as ineffective. Heating isoindolinone **247a** at reflux in either 6 M HCl or 1:1 4.5 M H_2SO_4:dioxane failed to give the hydrolyzed product in both cases. Finally, treating the isoindolinone **247a** with H_2O_2/LiOH at RT also failed to hydrolyze the lactam.

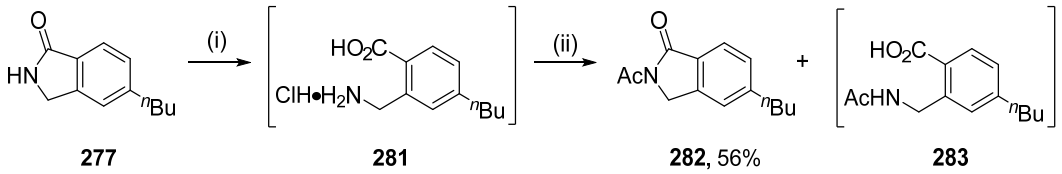


247a **280**

Scheme 39. Failed attempts at the hydrolysis of isoindolinone 247a. Reagents and conditions: (i) 1.0 M aq. NaOH, THF, 16 h, RT; (ii) 1.0 M aq. NaOH, 2-MeTHF, 16 h, RT; (iii) 1.0 M aq. NaOH, CPME, 16 h, RT; (iv) 1.0 M aq. NaOH, CPME, reflux, 3 days; (v) 1.0 M aq. NaOH, MeOH, 3 days, reflux; (vi) 6.0 M aq. HCl, 16 h, reflux; (vii) 1:1 4.5 M aq. H_2SO_4:dioxane, 8 h, reflux; 35% H_2O_2 in H_2O, LiOH, THF, 16 h, 0°C to RT.

Although there was no literature precedent for lactam-cleavage of an *N*-Bn isoindolinone, there is limited precedent for the acid-mediated ring-opening of an *N*-H isoindolinone.[154] Heating *N*-H isoindolinone **277** at reflux in 6.0 M aq. HCl for 16 h resulted in the formation of a product consistent with ring-opened salt **281** [crude ^{1}H NMR (400 MHz; DMSO-d_6); 4.28 (2H, q, J = 8.8, CH_2N)] (**Scheme 40**). Given the impracticalities associated with the purification, characterization and modification of hydrogen chloride salt **281** it was considered sensible to convert the compound *in situ* into an electronically neutral organic molecule. The reaction was repeated using 12 M aq. HCl and heated at reflux for 3 days. After this the volatile components were removed *in vacuo* and the crude product immediately treated with Ac_2O and NEt_3 in CH_2Cl_2. However, the major product of this reaction was *N*-Ac isoindolinone **282**. Evidence of ring-opened compound **283** was observed [crude ^{1}H NMR (400 MHz; DMSO-d_6); 8.20 (1H, t, J = 5.8, N*H*Ac), 4.82 (2H, d, J = 5.8, CH_2N)] but this compound was not isolated. Starting material **277** was also present in the crude product. Given the forcing reaction conditions and the challenges

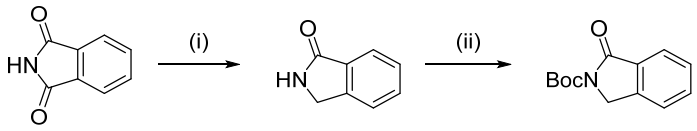
of functionalizing the ring-opened product, this line of inquiry was not pursued any further.



277 **281** **282**, 56% **283**

Scheme 40. Attempted cleavage of *N*-H lactam 277. Reagents and conditions: (i) 12 M HCl, reflux, 3 days; (ii) Ac_2O, NEt_3, CH_2Cl_2.

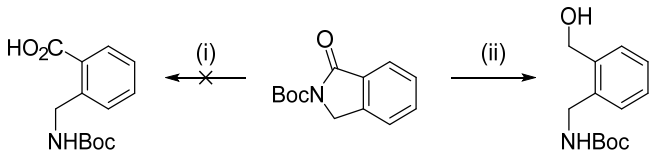
There is precedent for the hydrolytic ring-opening of an *N*-Boc isoindolinone,[155] so *N*-Boc isoindolinone **286** was prepared as a test substrate. Reduction of phthalimide **284** with metallic tin gave isoindolinone **285**,[156] which was treated with Boc_2O to form *N*-Boc isoindolinone **286** in 43% isolated yield over two steps (**Scheme 41**).[157]



284 **285** **286**
43% (2 steps)

Scheme 41. Preparation of *N*-Boc isoindolinone 286. Reagents and conditions: (i) Sn, HCl, reflux, 2 h; (ii) $(Boc)_2O$, DMAP.

The LiOH-mediated hydrolysis of *N*-Boc isoindolinone **286** proved to be ineffective, with no reaction observed (**Scheme 42**). However, with $NaBH_4$ the *N*-Boc isoindolinone **286** was reduced to the corresponding alcohol **288** in 65% isolated yield.[158] This represented an effective means of cleaving an isoindolinone lactam bond under practical reaction conditions to access a ring-opened product.

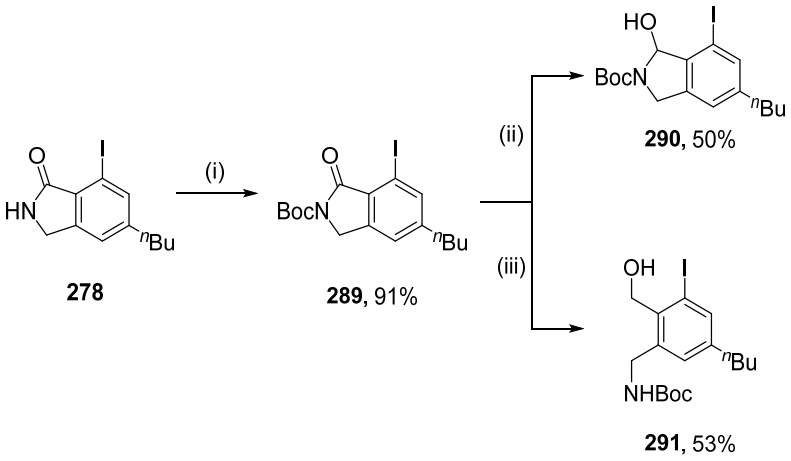


287 **286** **288**, 65%

Scheme 42. Attempts to ring-open *N*-Boc isoindolinone 286. Reagents and conditions: (i) aq. LiOH, THF; (ii) $NaBH_4$, H_2O, THF.

It was then necessary to apply the reductive cleavage conditions to a compound which had been prepared *via* the cyclization methodology (**Scheme 43**). Protection of *N*-H isoindolinone **278** resulted in the formation of the corresponding *N*-Boc isoindolinone **289** in 91% isolated yield. However, the conditions which were effective for the ring-

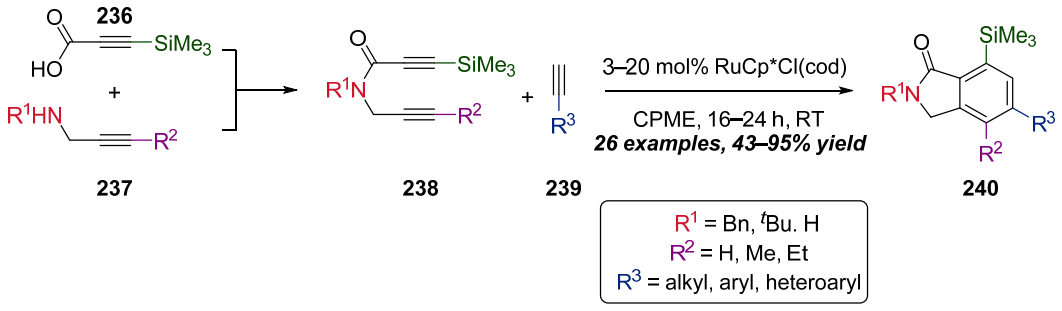
opening of test compound **286** were less effective on *N*-Boc isoindolinone **289**. The major product of this reaction was hemiaminal **290**, which was isolated in 50% yield. Target compound **291** was observed through analysis of the crude ^{1}H NMR spectrum, in addition to starting material **278**. When the reaction was repeated using $LiBH_4$ and MeOH in Et_2O the reaction reached completion and target alcohol **291** was formed in 53% yield.[159] A ^{1}H NMR spectrum of the unpurified product indicated that hemiaminal **290** was also formed during this reaction, with **290**:**291** = 1:2.



Scheme 43. Ring-opening of *N*-Boc isoindolinone 289. Reagents and conditions: (i) $(Boc)_2O$, DMAP; (ii) $NaBH_4$, H_2O, THF; (iii) $LiBH_4$, MeOH, Et_2O.

2.3. Chapter II Summary

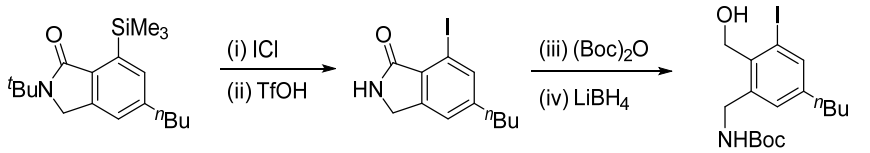
In conclusion, an efficient, selective and atom economical route to substituted isoindolinones *via* amide-tethered alkyne cyclotrimerizations has been established (**Scheme 44**). The key alkyne cyclotrimerization was conducted in CPME at RT with a commercial catalyst, so the reaction is readily transferable to a medicinal chemistry laboratory. Critically the solvent used for this reaction has a good environmental profile,[23] which is highly unusual for an alkyne cyclotrimerization.[105]



Scheme 44. Alkyne cyclotrimerization summary.

This approach has been used access a wide selection of isoindolinone products from readily accessible alkyne starting materials. The alkyne cyclotrimerization was effective with a selection of monoynes, including those with aliphatic and aromatic substituents. The reaction was also effective with a selection of different diynes, with various substituents at R^1 and R^2 (**Scheme 44**). Crucially, where R^2 = H, the reaction gave isoindolinone **240** as a single regioisomer.

It was also demonstrated that some of the cyclized products could be used as intermediates for the preparation of other synthetically interesting compounds (**Scheme 45**). It was shown that an aryl silane product could be converted to the corresponding aryl halide through *ipso*-substitution and that *N*-^{t}Bu isoindolinones could be converted in high yield to *N*-H isoindolinones through an acid-mediated deprotection. Finally it was demonstrated that this cyclization strategy could be used to access monocyclic benzene derivative **291** through reductive cleavage of the lactam.



267a **289**, 83% (2 steps) **291**, 48% (2 steps)

Scheme 45. Functional group manipulation of cyclization producted 267a.

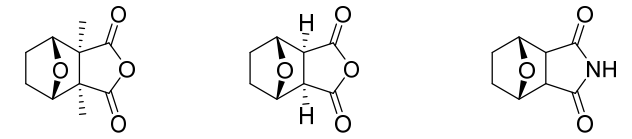
Chapter III. Irreversible *endo*-Selective Diels–Alder Reactions of Substituted Alkoxyfurans

3.1. Introduction

3.1.1. The Application of Cantharimides and Related Heterocycles in Medicinal Chemistry

Cantharidin

Cantharidin **301** (**Figure 8**) is a blister agent secreted as a defence by many species of blister beetle, including the Spanish fly (*Lytta vesicatoria*).[160] The natural product has reportedly been exploited in Chinese medicine under the name of Mylabris for the treatment of boils and piles since before the Common Era. Physicians in ancient Greece prescribed cantharidin as an aphrodisiac and it was used in that capacity by both Louis XV of France and Ferdinand II of Aragon.[161] Currently the only clinical application of the compound is as a 1% solution applied topically for the treatment of benign epithelial growths,[161] but where this compound has generated most interest is in the development of anticancer agents.[162] Cantharidin **301** has exhibited low μM activity against a selection of tumor cell lines, including cervical, colon, leukaemia, neuroblastoma and bone, although the cause of this cytotoxicity is not understood.[163] Cantharidin **301** is also highly toxic to humans, with the fatal dose believed to be less than 60 mg.[161]



cantharidin, **301** norcantharidin, **302** cantharimide, **303**

Figure 8. Cantharidin 301, norcantharidin 302 and cantharimide 303.

The high toxicity of cantharidin **301** has prevented any clinical exploitation as an antitumor agent, but it has inspired a new generation of structural analogues. Removing the two methyl groups gives norcantharidin **302**, which retains much of the antitumor activity with reduced renal and gastrointestinal toxicity (**Figure 8**).[164] Replacing the anhydride in norcantharidin with an imide led to the cantharimide skeleton **303**, which has been the focus of much interest within the medicinal chemistry community.

Cantharimides

Following on from the interest in cantharidin as an antitumor agent, substituted cantharimides have been investigated as potential cancer therapies (**Figure 9**).[165] For example, cantharimide **303a** was reported by Chan *et al*. and was shown to inhibit the growth of hepatoma cell line SK-Hep-1.[166] Cantharimide **303b** was developed as an inhibitor of androgen receptor signalling for the treatment of prostate cancer,[167] although it was abandoned following Phase I clinical trials. In addition, McCluskey *et al.* recently reported cantharimide **303c** with a GI_{50} value of 14–28 μM against eight different human cancer cell lines.[168] Substituted cantharimides have found applications outside of oncology,[169] in the development of positive allosteric modulators of the metabotropic glutamate receptor 4 (mGlu4),[170] as dynamin GTPase inhibitors[171] and as nematicides.[172]

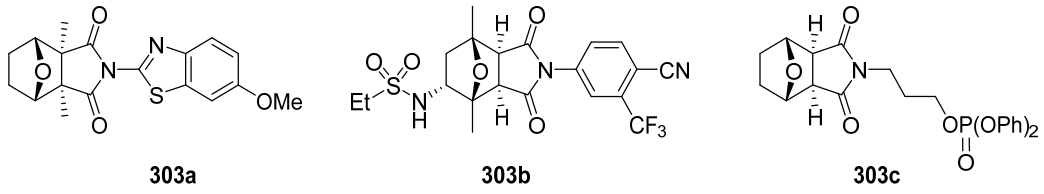


Figure 9. Cantharimides developed as an antitumor agents.

Oxabicyclo[2.2.1]heptane derivatives

The cantharimide is based upon the oxabicyclo[2.2.1]heptane scaffold, and this scaffold has been used more widely within medicinal chemistry (**Figure 10**).[162, 163, 173] For example, oxabicyclo[2.2.1]heptane **304a** (a ring-opened derivative of a cantharimide) is an antiplasmodial agent that inhibits D6 and W2 *Plasmodium falciparum* malarial strains with low μM activity.[169b] Compound **304b** was developed as an inhibitor of protein phosphatase 1 (IC_{50} = 48 ± 9 μM) that is modestly selective over protein phosphatase 2a (IC_{50} = 85 ± 3 μM).[174] Sulfonate **304c** was developed as a ligand for the estrogen receptor, which functioned as an antagonist for subtypes ERα and ERβ with good affinity.[175] Dhanapal *et al.*[176] have reported ketone **304d** as a novel antibiotic. It has a MIC (minimum inhibitory concentration) of 0.004 mg mL^{-1} against *Klebsiella pneumonia* (compared to MIC = 0.007 mg mL^{-1} for ciprofloxacin) but it lacked good activity against a broad spectrum of bacteria. In addition, 7-oxabicyclo[2.2.1]heptane derivatives are valuable intermediates for synthetic chemistry[177] and the scaffold can be found in a number of natural products beyond cantharidin.[178]

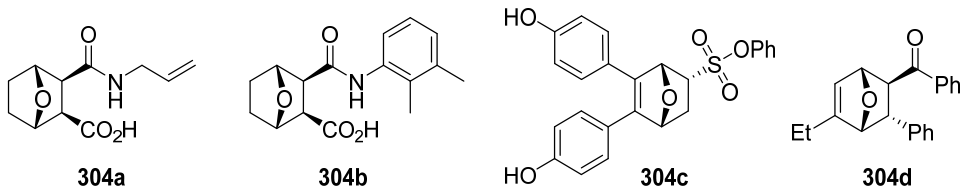
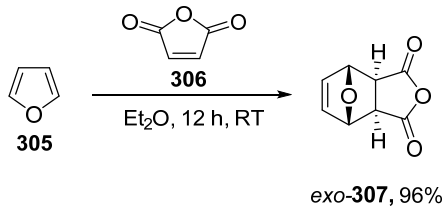


Figure 10. Examples of biologically active oxabicyclo[2.2.1]heptane derivatives.

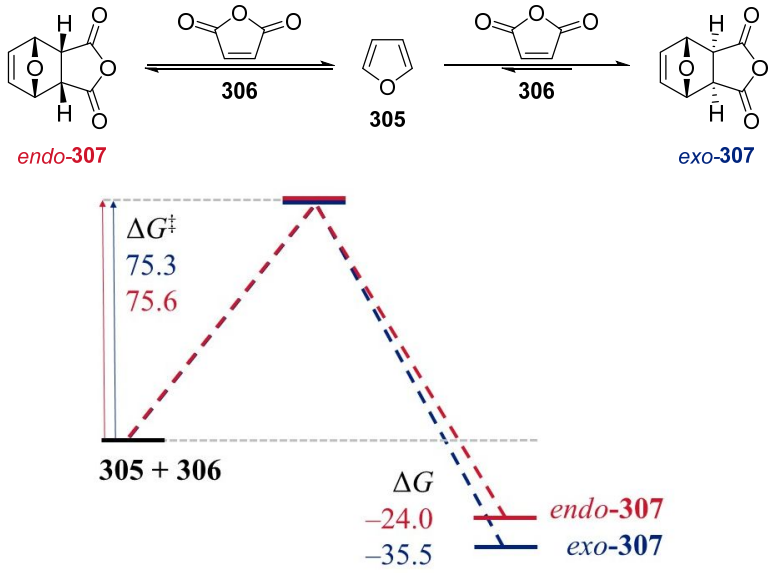
3.1.2. [4+2]-Cycloaddition Reactions of Furans and Dienophiles

The most exploited route to oxabicyclo[2.2.1]heptane derivatives is *via* the [4+2]-cycloaddition of furans and dienophiles. Following the pioneering work of Diels and Alder,[179] the most widely studied example of a furan [4+2]-cycloaddition is the reaction of furan with maleic anhydride.[180] This reaction is known to be thermodynamically controlled, ultimately giving *exo*-**307** as a single diastereoisomer. (**Scheme 46**).[181]



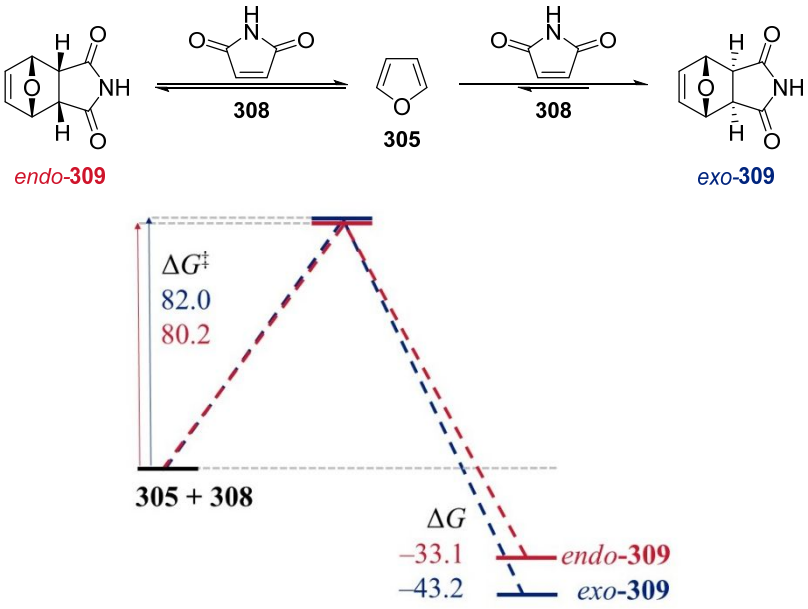
Scheme 46. [4+2]-Cycloaddition of furan 305 and maleic anhydride 306.[181]

Svatoš *et al.* explored the reaction of furan **305** with maleic anhydride **306** computationally using MP2/6-31+G(d) equilibrium geometries.[182] They calculated a small difference in activation energy for *endo*- and *exo*-cycloadditions but a significantly lower ΔG for the formation of *exo*-**307** (**Scheme 47**). This, along with the small barrier to the retro-cycloaddition reaction, explains why any *endo*-**307** formed under the reaction conditions readily isomerizes to give exclusively *exo*-**307**.



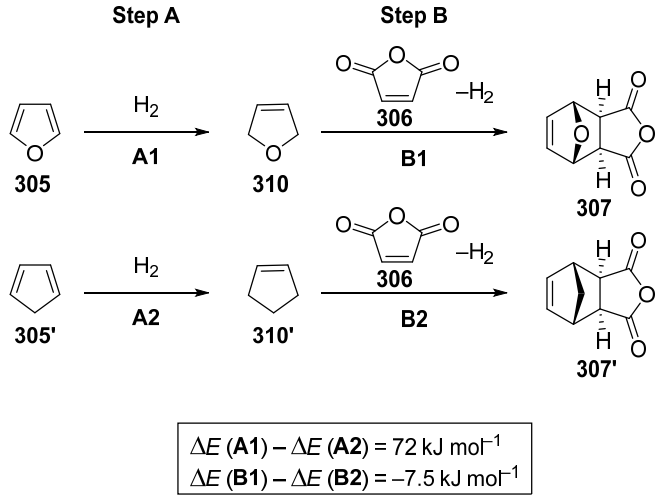
Scheme 47. Free energy diagram for the reaction of furan and maleic anhydride.[182] Data calculated for reactions in MeCN at 25 °C using the MP2/6-31+G(d) level of theory. All values in kJ mol^{-1}.

The reaction of furan **305** with maleimide **308** was also explored experimentally and computationally by Svatoš *et al*. As part of their study, a purified sample of *endo*-**309** was dissolved in MeCN-d_3 and it was observed to undergo a rapid decomposition at 65 °C to give furan **305**, maleimide **308** and *exo*-**309**. This experiment suggested that the cycloaddition of furan **305** and maleimide **308** was reversible, with *exo*-**309** the thermodynamic product. This hypothesis was supported by computational calculations, with the data illustrated in **Scheme 48**.



Scheme 48. Free energy diagram for the reaction of furan and maleimide.[182] Data calculated for reactions in MeCN at 25 °C using the MP2/6-31+G(d) level of theory. All values in kJ mol^{-1}.

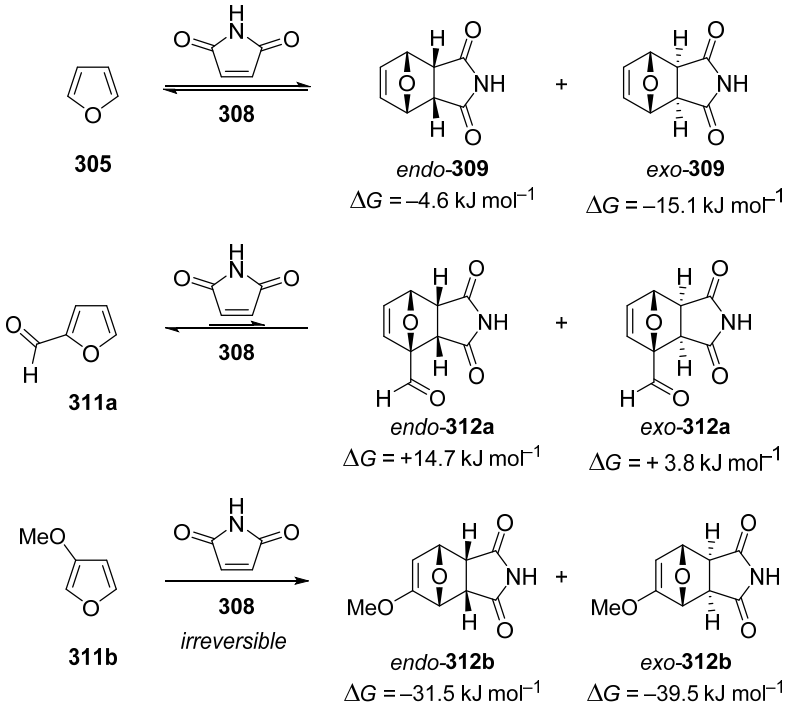
The reversibility of furan-Diels–Alder reactions is in contrast with the corresponding reactions of cyclopentadiene, which undergoes a rapid and irreversible reaction with both maleic anhydride and maleimide. A reasonable justification for this is the loss of aromaticity that occurs when furan undergoes a cycloaddition reaction, which is not observed where cyclopentadiene is the dienophile. Svatoš explored this with use of two thermodynamic cycles detailed in **Scheme 49**.[182] The total reaction free energy ΔE for the partial hydrogenation of furan **305** to give 2,5-dihydrofuran **310** was 72 kJ mol^{-1} greater than the corresponding reaction of cyclopentadiene **305'**. In contrast, the difference in ΔE for the second step of the two thermodynamic cycles was only 7.5 kJ mol^{-1}. This supported the theory that it is the dearomatization of furan **305** that reduces the thermodynamic driving force for the [4+2]-cycloaddition reaction with maleic anhydride **306**, which contributes to the reversible nature of the reaction.



Scheme 49. Thermodynamic cycle involving the hydrogenation of furan and cyclopentadiene.[182] Data calculated using DFT(B3LYP)/6-311++G(2d,p) level of theory.

In 2011 Boutelle and Northrop published computational and experimental work on the reaction between substituted furans and maleimide.[183] They demonstrated that different substituents at the 2- and 3-position had a dramatic impact on equilibrium position for the cycloaddition reaction (**Scheme 50**). The reaction of maleimide **308** and furan **305** was calculated to have a low thermodynamic driving force for both *exo*- and *endo*-diastereoisomers and it was shown experimentally that the reaction was reversible at 25 °C in MeCN. The reaction of furfural **311a** with maleimide **308** was less favorable, with the equilibrium favoring the free furan. However, the reaction of 3-methoxyfuran **311b** and maleimide **308** was calculated to have a significant thermodynamic driving

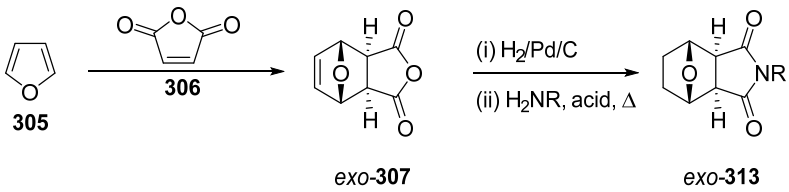
force and the authors suggested that this would be an irreversible cycloaddition reaction. This reaction was not attempted experimentally.



Scheme 50. The calculated effect of furan substituents on a furan Diels–Alder reaction. All values calculated for reactions in MeCN at 25 °C using the MP2/6-311+G(d,p) level of theory for single-point electronic energies and the the CBS-QB3 level of theory for vibrational frequency analysis.

3.1.3. The Synthesis of Cantharimides and Other Oxabicyclo [2.2.1] heptane Derivatives

The majority of cantharimides that have been prepared in medicinal chemistry programs have been accessed *via* the [4+2]-cycloaddition of furans and maleic anhydride.[184] Reduction of the alkene unit followed by condensation with a primary amine gives the corresponding *exo*-cantharimide as a single diastereoisomer (**Scheme 51**).

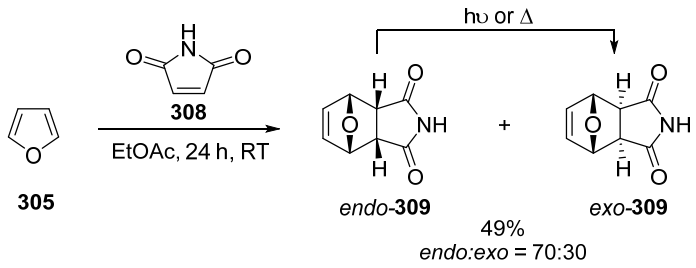


Scheme 51. Synthesis of cantharimide *exo*-313 from anhydride *exo*-307.

This approach has been applied to prepare large numbers of *N*-substituted cantharimides, however the approach is not well suited to varying substitution about the carbon framework. There are relatively few examples of *exo*-cantharimides being prepared from furans bearing substituents other than alkyl groups. A notable limitation is that there are

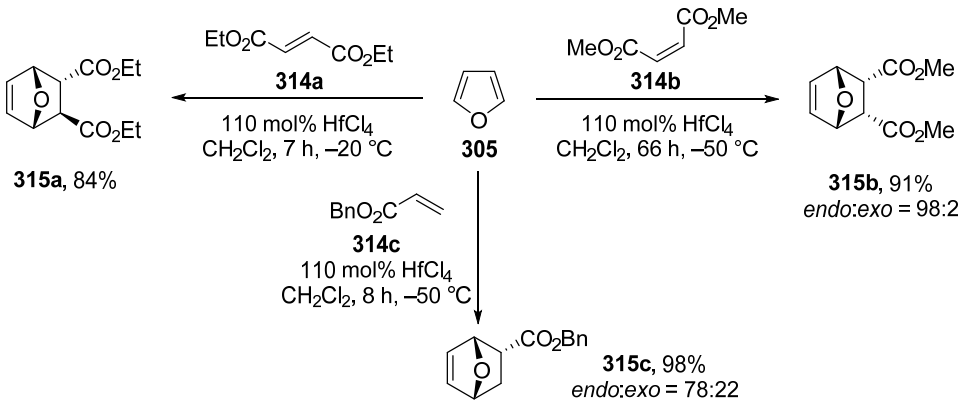
no reported examples of 2-aryl or 2-heteroarylfurans undergoing furan-Diels–Alder reactions with dienophiles *of any type*.

A less popular and more challenging route to cantharimides is *via* the [4+2]-cycloaddition of furans and maleimides (**Scheme 52**).[182] As described in the previous section, this reaction is under thermodynamic control at RT, but equilibration is relatively slow and it is possible to isolate both *endo*-and *exo*-cantharimide **309** from a reaction mixture. However, cantharimide *endo*-**309** was reported by Kwart and Burchuk to rapidly isomerize in either hot solvent or under visible light irradiation.[185] As such there is no practical route to access *endo*-cantharimides through [4+2]-cycloaddition reactions and the scaffold has not been widely reported.[186]



Scheme 52. [4+2]-cycloaddition of furan 305 and maleimide 308.

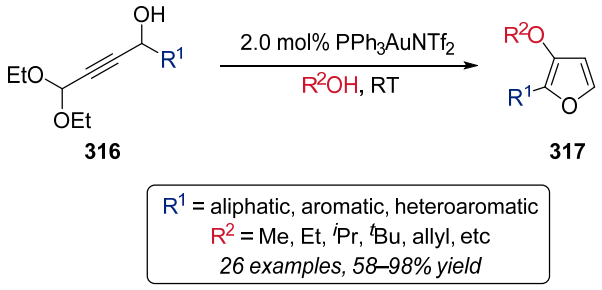
The [4+2]-cycloaddition of furan with dienophiles other than maleic anhydride and maleimides are known, although these reactions typically require either elevated pressures[187] or Lewis acid catalysts.[188] The most general set of conditions for the [4+2]-cycloaddition of furans with various dienophiles were developed by Hayashi *et al*. and relied upon $HfCl_4$ as a Lewis acid catalyst (**Scheme 53**).[189] Under these conditions diethyl fumarate **314a** and dimethyl maleate **314b** could be converted into the corresponding furan adducts and in the latter case with excellent *endo*-selectivity. Furan **305** also underwent a [4+2]-cycloaddition with benzyl acrylate **314c** to give oxabicyclo[2.2.1]heptene **315c** in excellent yield. However, in order to achieve this 110 mol% $HfCl_4$ was required and furan **305** was used in twenty-fold excess. In some cases reactions were also conducted using only 20 mol% $HfCl_4$ but this resulted in reduced diastereoselectivity and/or reduced isolated yield. There was also a limited scope of furans used in this study, with only furan, 2-methylfuran and 2,5-dimethylfuran considered.



Scheme 53. $HfCl_4$-caltalyzed [4+2]-cycloaddition of furan and various dienophiles.[189]

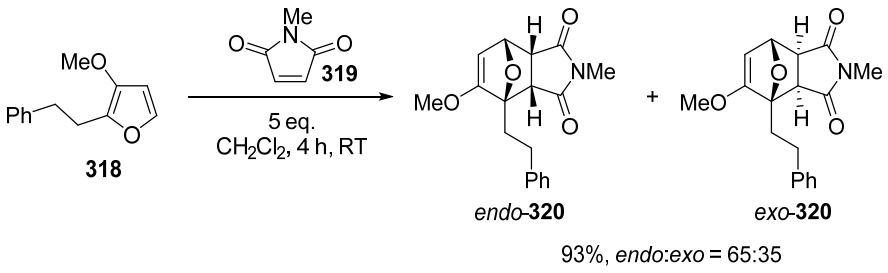
3.1.4. The Synthesis and Application of 3-Alkoxyfurans

Recent work within the Sheppard laboratory on the gold-catalyzed transformation of propargylic alcohols has led to an efficient synthesis of 3-alkoxyfurans, as summarized in **Scheme 54**.[190] Treatment of propargylic alcohol **316** with 2.0 mol% PPh_3AuNTf_2 in an alcohol solvent gave 3-alkoxyfuran **317** in 58–98% yield. The reaction had a broad substrate scope both with regard to substituent R^1 and the alcohol solvent.



Scheme 54. Summary of a 3-alkoxyfuran synthesis as developed by Sheppard *et al.*[190]

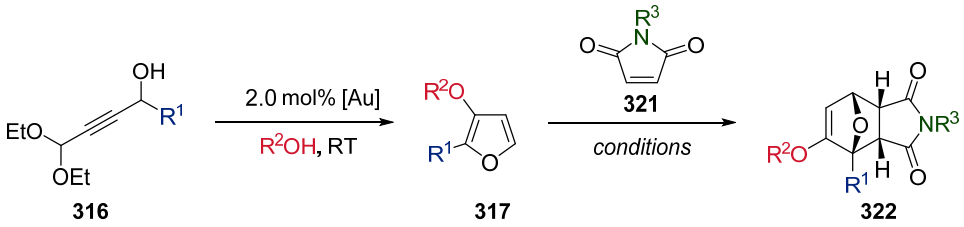
Prior to the above work there was no efficient route into 3-alkoxyfurans and so there is little reported precedent for these compounds being used as dienes in a cycloaddition reaction.[191] It was shown that furan **318** underwent a [4+2]-cycloaddition reaction with *N*-methylmaleimide **319** at RT to give the corresponding adduct **320** as a mixture of diastereoisomers in 93% combined isolated yield (**Scheme 55**).



Scheme 55. [4+2]-Cycloaddition of furan 318 and *N*-methylmaleimide 319.[190]

3.1.5. Chapter III Project Outline

The cantharimide is a valuable scaffold for drug development but the preparation of highly substituted cantharimides presents a major synthetic challenge. The aim of this part of the PhD was to explore the reaction of 2-substitued 3-alkoxyfurans **317** and maleimides **321** as a novel route to substituted cantharimides (**Scheme 56**). The synthesis of *endo*-cantharimides was of particular interest given that this scaffold was broadly unexplored within medicinal chemistry. It was important that the conditions developed for the [4+2]-cycloaddition used sustainable solvents, in order to minimize the waste generated by the synthetic route.



Scheme 56. Proposed synthetic route to highly-substituted *endo*-cantharimides.

Another goal for this chapter was to prepare a more diverse range of heterocycles by using dienophiles other than maleimides, such as maleates, enones and acrylates (**Figure 11**). This would allow access to new classes of 7-oxabicyclo[2.2.1]heptane derivatives. It was also identified that aromatization of the furan-Diels–Alder products would generate highly substituted benzene-derivatives, such as phthalimides **323c**.

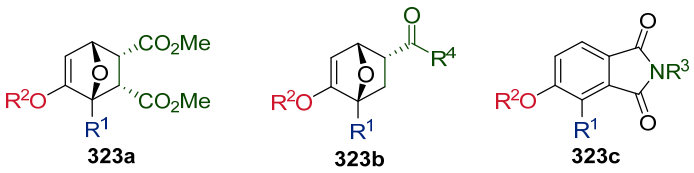


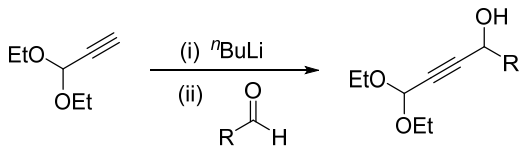
Figure 11.Other heterocycles of interest.

3.2. Results and Discussion

3.2.1. Starting Material Synthesis

Preparation of Propargylic Alcohols

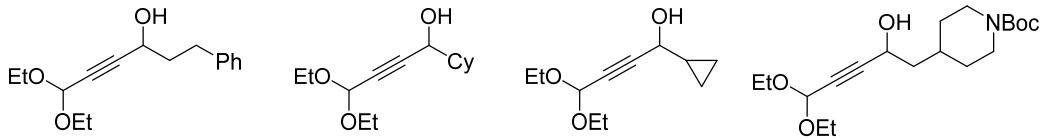
A number of propargylic alcohols **316** were prepared by a general procedure from commercial alkyne **324**, as precursors to 3-alkoxyfurans.[190] The general procedure is summarized in **Scheme 57**.



324 **316**

Scheme 57. General procedure for the preparation of propargylic alcohols 316. Reagents and conditions: (i) ^{n}BuLi, THF, 1 h, –78 °C; (ii) RCOH, 16 h, –78 °C to RT

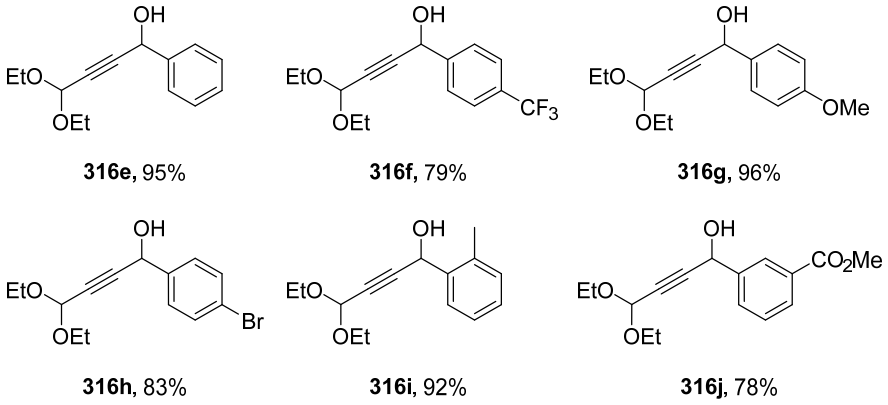
Initially four propargylic alcohols were prepared from aldehydes with adjacent sp^3-centres in 71–86% yield (**Figure 12**). The reaction procedure was effective for preparing multi-gram quantities of product, with alcohol **316a** synthesized from hydrocinnamaldehyde on a 60.0 mmol scale to give 12.8 g of product. The reaction tolerated both a cyclopropyl substituent and an *N*-Boc piperidine to give alcohols **316c** and **316d** respectively.



316a, 81% **316b**, 86% **316c**, 83% **316d**, 71%

Figure 12. Propargylic alcohols prepared from aliphatic aldehydes.

The general procedure was effective with a range of benzaldehyde derivatives to give propargylic alcohols bearing aromatic substituents in 78–96% yield (**Figure 13**). The reaction was again effective on a multi-gram scale; 10.5 g of alcohol **316e** was prepared from benzaldehyde in 95% yield. The reaction tolerated electron-deficient (**317f** and **317j**) and electron-rich arenes (**316g**) as well as an aryl bromide (**316h**) and a sterically encumbered arene (**316i**).

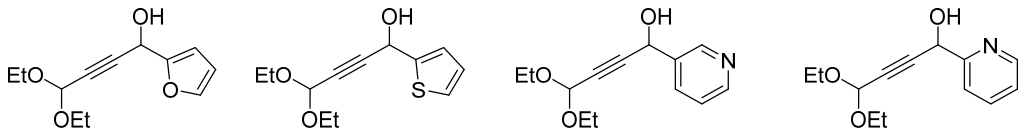


316e, 95% **316f**, 79% **316g**, 96%

316h, 83% **316i**, 92% **316j**, 78%

Figure 13. Propargylic alcohols prepared from aromatic aldehydes.

Furthermore, it was possible to prepare propargylic alcohols bearing furan and thiophene substituents using the general procedure, as shown in **Figure 14**. While 3-pyridyl alcohol **316m** was isolated in 70% yield by this approach, two separate attempts to access 2-pyridyl alcohol **316n** gave only a complex mixture of unidentified products.

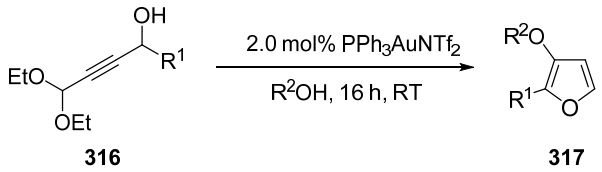


316k, 86% **316l**, 49% **316m**, 70% **316n**, 0%

Figure 14. Propargylic alcohols bearing heteroaromatic substituents prepared by the general procedure.

Preparation of 3-Alkoxyfurans

According to the method previously developed within the Sheppard Laboratory, 3-alkoxyfurans **317** were prepared from the corresponding propargylic alcohol **316** by a gold(I)-catalyzed cyclization (**Scheme 58**).[190] The choice of alcohol solvent determined the alkoxy-substitution in the product.

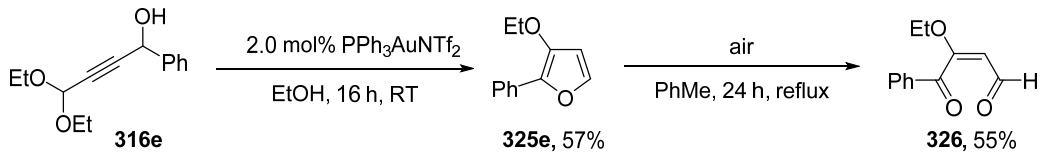


316 **317**

Scheme 58. General synthesis of 3-alkoxyfurans.[190]

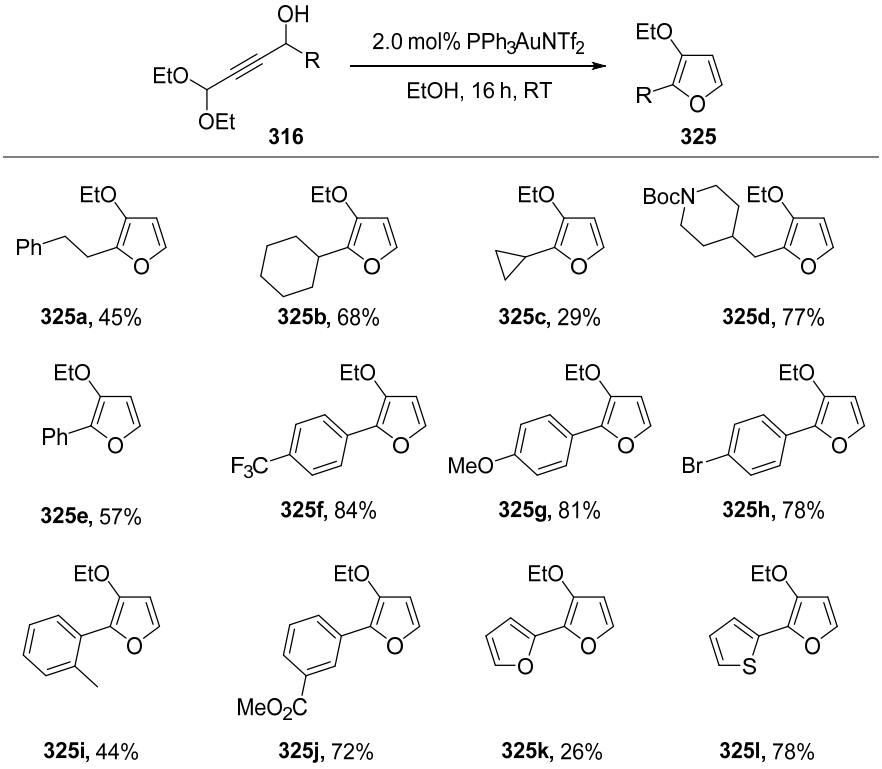
In general, the 3-alkoxyfurans were found to be relatively volatile and this made isolating these compound in good yield challenging. For this reason it was found generally best to avoid a work up and simply purify the reaction mixture (with solvent) directly by flash column chromatography. In order to avoid significant loss of product upon concentration the furans were purified using petroleum ether with a boiling point in the range 30–40 °C, along with TBME. The solvent was then removed using a rotary evaporator water bath at 0 °C at >100 mbar pressure.

Another challenge when isolating 3-alkoxyfurans was that they were liable to oxidize in the presence of atmospheric oxygen. This was a second reason for cooling the rotary evaporator water bath to 0 °C; furans were observed to oxidize on the rotary evaporator even at RT. It was generally necessary to use the furans as soon as they were prepared. In order to characterize the oxidation, furan **325e** was heated in PhMe under an atmosphere of air and aldehyde **326** was isolated in 55% yield following purification (**Scheme 59**).



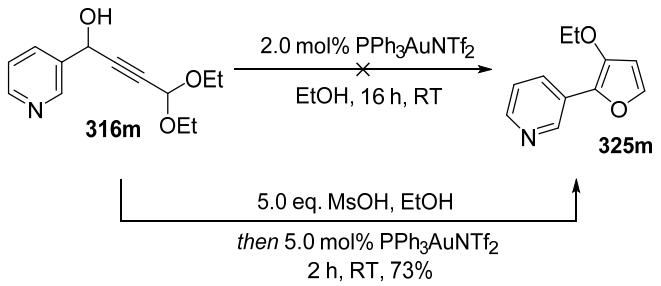
Scheme 59. Aerobic oxidation of furan 325e.

With the precautions described above, a selection of 3-ethoxyfurans **325** were isolated in 26–84% yield (**Scheme 60**). Both furans **325a** and **325e** were prepared using 2.00 g of the corresponding alcohol. The reaction was tolerant of a number of aliphatic substituents, most notably an *N*-Boc piperidine to give furan **325d** in 77% yield. The reaction was also tolerant of a range of electron-rich, electron-poor and sterically encumbered aromatic substituents. Heteroaromatic substituents could also be accommodated, with bisfuran **325k** and thiophene **325l** prepared. The yields for bisfuran **325k** and 2-cyclopropyl furan **325c** were poor (26% and 29% respectively), which is likely due to their exceptionally high volatility.



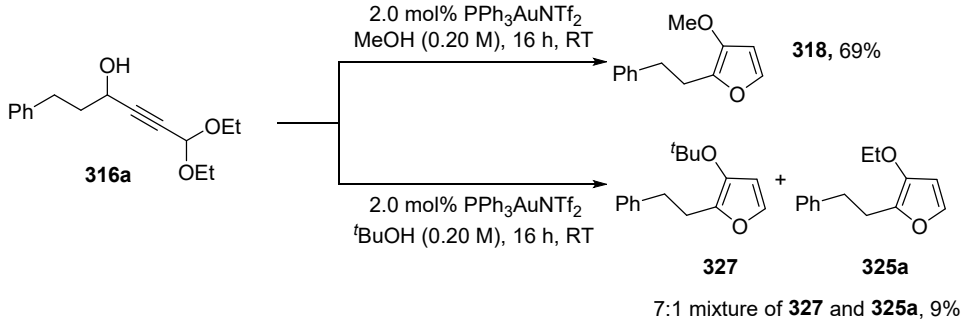
Scheme 60. General synthesis of 3-ethoxyfurans 325.

In contrast to the above reactions, pyridine **316m** underwent no reaction when it was treated with EtOH and 2.0 mol% $PPh_3Au(I)NTf_2$ (**Scheme 61**). However, when 5.0 eq. of MsOH was added to the reaction mixture before the gold catalyst a reaction was observed, with furan **325m** isolated in 73% yield.



Scheme 61. Synthesis of 2-pyridyl furan 325m.

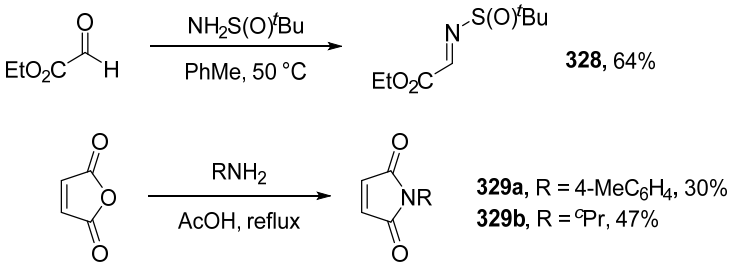
The reaction was also conducted in other solvents to access furans with different alkoxy groups. Conducting the reaction at 0.50 M concentration in MeOH resulted in the formation of the desired 3-methoxyfuran **318** but with a small 3-ethoxyfuran impurity. However, this side product was avoided by diluting the reaction to 0.20 M (**Scheme 62**). These conditions could not be applied to the efficient synthesis of the analogous *tert*-butyl alkoxyfuran **327**. Conducting the reaction in ^{t}BuOH gave the desired furan but in very low yield and with a 3-ethoxyfuran impurity.[190]



Scheme 62. Synthesis of 3-alkoxyfurans from different alcohols.

Synthesis of Dienophiles

The majority of dienophiles used in this work were purchased from commercial sources, but three compounds were prepared using literature procedures (**Scheme 63**). Imine **328** was prepared in 64% isolated yield by the condensation of ethyl 2-oxoacetate and (±)-*tert*-butyl sulfinamide.[192] Maleimides **329a** and **329b** were made from maleic anhydride in poor yield (30% and 47% respectively) but on a gram scale.[193]

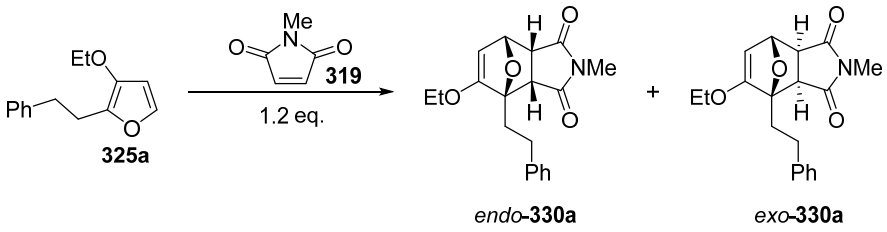


Scheme 63. Synthesis of dienophiles.

3.2.2. Synthesis of Cantharimides *via* the [4+2]-Cycloadditions of 3-Alkoxyfurans

The [4+2]-cycloaddition reaction of furan **325a** and *N*-methylmaleimide **319** was found to proceed efficiently at RT in Et_2O, PhMe, EtOH and dimethyl carbonate (DMC) (**Table 13**, Entries 1–4). The *endo*- and *exo*-diastereoisomers of cantharimide **330a** were identified by coupling constant analysis of the ^1H NMR spectra, as discussed in the following paragraph. DMC was selected as a solvent for further work as it resulted in the highest *endo*-selectivity (Entry 4) and because of its excellent environmental profile.[23] It was possible to remove the small excess of *N*-methylmaleimide **319** by flushing the reaction mixture through an aminopropyl cartridge, giving cantharimide **330a** in 93% yield as a 70:30 mixture of *endo*- and *exo*-diastereoisomers (Entry 4). This reaction was scaled up to use 1.00 g of furan **325a** with no significant impact on yield or selectivity (Entry 5). Cooling the reaction down to 0 °C had little effect on diastereoselectivity, with cantharimide **330a** isolated as a 75:25 mixture of *endo*- and *exo*-diastereoisomers (Entry 6). Heating the reaction at 80 °C for 16 h reduced the diastereoselectivity, with cantharimide **330a** isolated with an *endo*:*exo* ratio of 45:55 (Entry 7). Heating at the same temperature over 3 days gave cantharimide **330a** with a small selectivity for *exo*-**330a** but in only 40% isolated yield (Entry 8). The conditions in Entry 4 were selected as the optimized reaction conditions for further studies into furan-Diels–Alder reactions.

Table 13. [4+2]-Cycloaddition of furan 325a and *N*-methylmaleimide 319.



Entry	Solvent	Temperature/°C	Time/h	Yield **330a**/%	*endo*:*exo*[a]
1	Et_2O	25	4	98[b]	65:35
2	PhMe	25	4	100[b]	65:35
3	EtOH	25	4	100[b]	70:30
4[d]	**DMC**	**25**	**4**	**93**[c]	**70:30**
5[e]	DMC	25	4	95[c]	75:25
6	DMC	0	6	93[c]	75:25
7	DMC	80	16	93 [c]	55:45
8	DMC	80	72	40[c]	45:55

[a] Determined by analysis of the crude ^{1}H NMR spectrum. [b] Yield determined by ^{1}H NMR spectroscopy using pentachlorobenzene as an internal standard. [c] Isolated yield. [d] Reaction conducted with 108 mg of furan **325a**. [e] Reaction conducted with 1.00 g of furan **325a**.

For the reactions in Table 13 the diastereoselectivity of the formation of cantharimide **330a** was determined by analysis of the ^{1}H NMR spectra. It was observed that the coupling constant between the bridgehead proton H^a and the adjacent proton H^b, $J_{(Ha-Hb)}$ = 5.3 Hz (Figure 15). This was consistent with the *endo*-diastereomer, where the dihedral angle between H^a and H^b was calculated at 36.6 °.[194] In contrast, there was no measurable coupling measured between the corresponding protons for the minor diastereomer. This is consistent with *exo*-**330a**, where the dihedral angle between H^a and H^b was calculated as 80.6 °. This coupling constant analysis was used to assign the diastereoselectivity of furan-Diels–Alder reactions throughout this study.

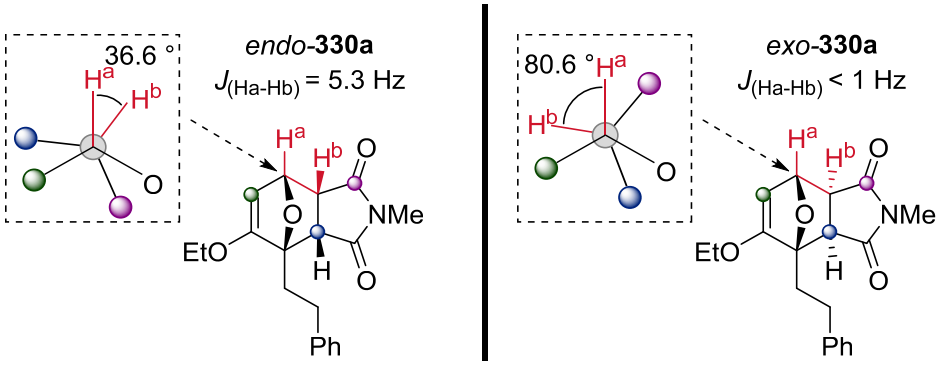
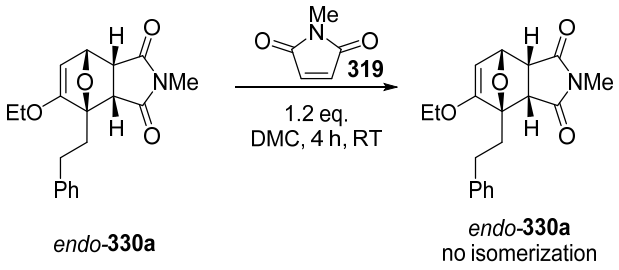


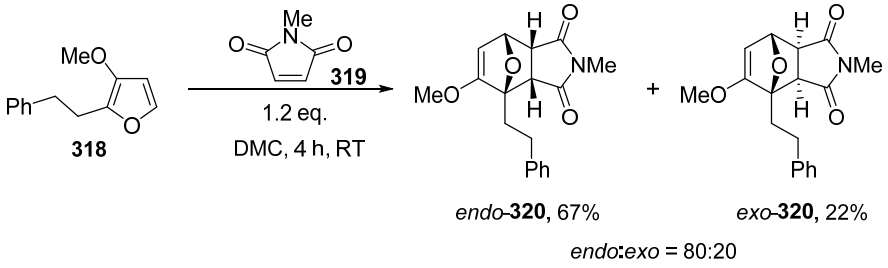
Figure 15. Determining diastereoselectivity by coupling constant analysis.

An important question regarding the [4+2]-cycloaddition of 3-alkoxyfuran **325a** and *N*-methylmaleimide **319** at RT was whether the reaction was under kinetic control. The *endo*- and *exo*-diastereoisomers of cantharimide **330a** were separated by flash column chromatography and treating *endo*-**330a** under the replicated reaction conditions resulted in no isomerization (**Scheme 64**). This observation is consistent with a kinetically controlled Diels–Alder reaction.



Scheme 64. Furan-Diels–Alder reversibility study.

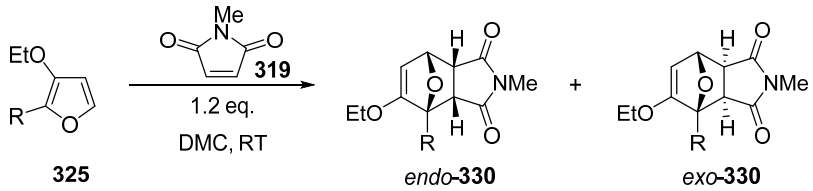
The optimized furan-Diels–Alder reaction conditions (**Table 13**, Entry 4) were applied to the reaction of 3-methoxyfuran **318** and *N*-methylmaleimide **319** (**Scheme 65**). Coupling constant analysis of the crude ^{1}H NMR spectrum confirmed that the reaction was *endo*-selective (*endo*:*exo* = 80:20). Following flash column chromatography the two diastereoisomers of cantharimide **320** were isolated separately in 89% combined yield.

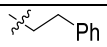
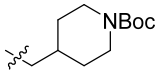
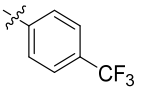
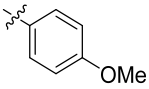
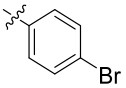
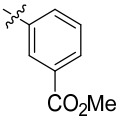


Scheme 65. [4+2]-Cycloaddition of furan 318 and *N*-methylmaleimide 319.

The optimized furan-Diels–Alder reaction conditions were applied to the reaction of *N*-methylmaleimide **319** and different 3-ethoxyfurans **325** (**Table 14**). The [4+2]-cycloaddition reaction was found to be effective with a range 3-ethoxyfurans with aliphatic substituents (Entries 2–4). Cantharimides were isolated in 85–95% yield with reasonable *endo*-selectivity.

Table 14. [4+2]-Cycloadditions of different 3-ethoxyfurans 325 with *N*-methylmaleimide 319.



Entry	R	Product	Time/h	Isolated yield **330**/%	*endo*:*exo*[a]
1		**330a**	4	93	70:30
2		**330b**	4	95	85:15
3		**330c**	4	90	80:20
4		**330d**	4	85	75:25
5		**330e**	6	86 (86)[b]	80:20
6		**330f**	24	75	80:20
7		**330h**	4	90	80:20
8		**330g**	24	78	80:20
9		**330i**	24	86	75:25
10		**330j**	24	83	80:20
11		**330k**	24	85	90:10
12		**330l**	24	96	70:30
13		**330m**	24	92	70:30

[a] As determined from a ^{1}H NMR spectrum of the crude product. [b] Conducted using 1.00 g of furan **325e**.

The reaction was also conducted with a range of aromatic substituents, giving the cantharimide product **330** in 75–90% isolated yield and with a consistent *endo*-diastereoselectivity (**Table 14**, Entries 5–10). As such these represent the first reported examples of furan-Diels–Alder reactions using 2-arylfurans. The reaction tolerated an electron rich aromatic substituent (Entry 7), an aryl bromide substituent (Entry 8), electron poor aromatic substituents (Entries 6 and 10) and a sterically hindered substituent (Entry 9). Isomerically pure samples of *endo*-**330e** and *exo*-**330e** were recrystallized from

CH_2Cl_2/hexane and the relative stereochemistry of both diastereoisomers were confirmed by single crystal X-ray diffraction (**Figure 16**).[i]

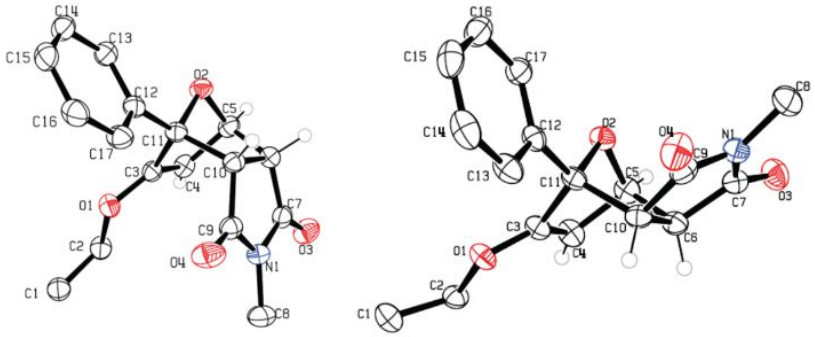
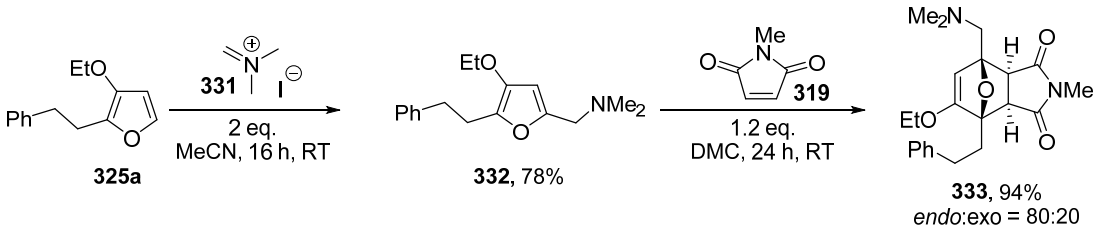


Figure 16. Crystal structures of cantharimides *endo*-330e (left) and *exo*-330e (right). Ellipsoids are shown at 50% probability level. Only hydrogen atoms belonging to the cyclic core are shown for clarity.

The furan-Diels–Alder reaction was also successful for furans with heteroaromatic substituents, as seen in Entries 11 to 13 of **Table 14**. The 2-furyl example shown in Entry 11 is an excellent demonstration of the strength of this strategy for accessing cantharimides, as the cycloaddition reaction occurred with high chemoselectivity for the 3-alkoxyfuran over the 3-H furan substituent.

Another substituent was incorporated into the cantharimide skeleton *via* substituent at the 5-position of the 3-alkoxyfuran (**Scheme 66**). Treating 3-alkoxyfuran **325a** with Eschenmoser's salt **331** in MeCN resulted in the formation of furan **332** in 78% yield. Under the standard cyclization conditions cantharimide **333** was formed in 94% yield after 24 h as an 80:20 mixture of *endo*- and *exo*-diastereoisomers.



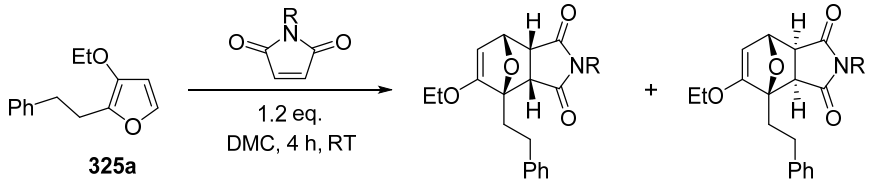
Scheme 66. Preparation of a 5-substituted 3-alkoxyfuran and subsequent [4+2]-cycloaddition.

The furan-Diels–Alder conditions could also be applied to reactions using other *N*-substituted maleimides, as shown in **Table 15**. The reaction was effective when the maleimide possessed a phenyl, benzylic or cyclopropyl substituent, with the

[i] Dr Dejan-Krešimir Bučar and Dr Laure Benhamou are gratefully acknowledged for conducting and analyzing the single crystal X-ray diffraction experiment. Recrystallization was performed by the author.

cantharimides **334** isolated in 83–94% yield. Interestingly, while *N*-substitution had no notable effect on reaction time, substitution had a clear effect on diastereoselectivity. In particular, the reaction to form cantharimides **334b** (Entry 2) lacks the clear *endo*-selectivity previously seen for the reaction of 3-alkoxyfurans **325** with *N*-methylmaleimide **319** (**Table 14**). This may be explained by the additional steric bulk at the *N*-terminus, which would increase unfavorable steric interactions in the *endo*-transition state.

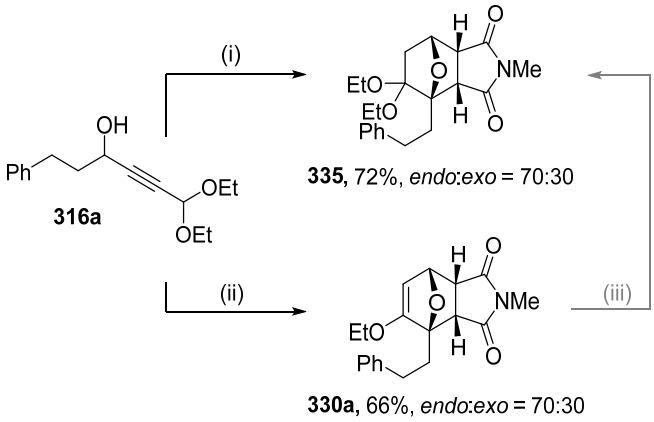
Table 15. [4+2]-Cycloaddition of furan 325a with *N*-substituted maleimides.



Entry	R	Product	Isolated yield/%	*endo*:*exo*[a]
1	Ph	**334a**	94	65:35
2	4-MeC_6H_4	**334b**	83	55:45
3	^{c}Pr	**334c**	87	60:40

[a] As determined from a ^{1}H NMR spectrum of the crude product.

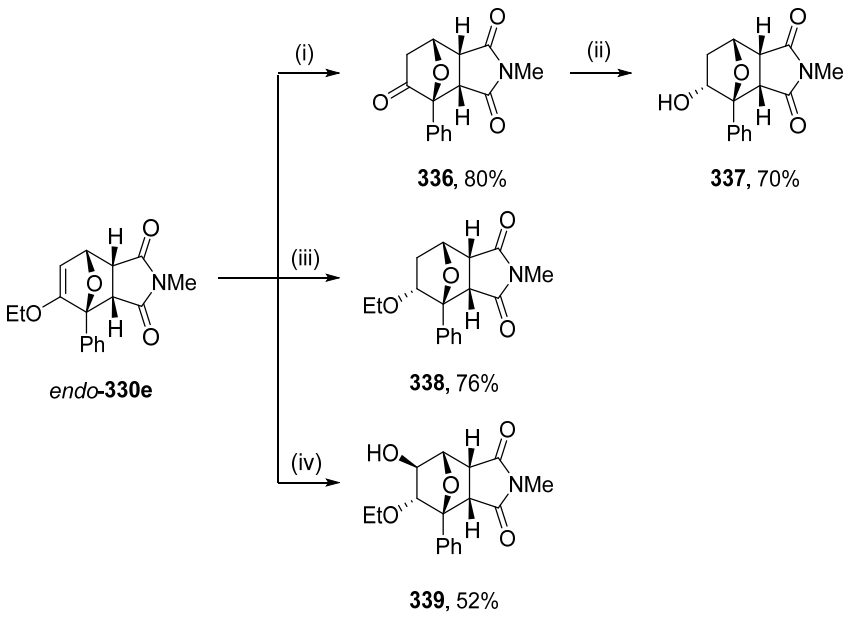
The cycloaddition reaction and the furan synthesis were combined into in a single step to generate a cantharimide directly from propargylic alcohol **316a** (**Scheme 67**). However, rather than forming enol ether **330a** as has been observed previously, the isolated product was diethyl acetal **335**. This implied that the direct furan-Diels–Alder product **330a** underwent a solvolysis reaction under the reaction conditions. However, enol ether **330a** was formed in a one-pot procedure from propargylic alcohol **316a** by: a) treating alcohol **316a** with 2.0 mol% PPh_3AuNTf_2 in EtOH; b) addition of 2.5 mol% PPh_3 upon 100% conversion of alcohol **316a and**; c) addition of *N*-methylmaleimide **319** after a further 1 h. By following this procedure acetal formation was avoided and enol ether was **330a** isolated in 66% yield. This result suggested that the gold catalyst was responsible for the acetal formation and that the catalyst was deactivated using PPh_3. This rationale was tested by treating enol ether **330a** with 2.0 mol% PPh_3AuNTf_2 in EtOH, which resulted in the efficient formation of diethyl acetal **335**.



Scheme 67. One-pot cantharimide synthesis from propargylic alcohol 316a.Reagents and conditions: (i) *N*-methylmaleimide **319**, 2.0 mol% PPh_3AuNTf_2, EtOH, 16 h, RT; (ii) 2.0 mol% PPh_3AuNTf_2, EtOH, 3 h, RT then 2.5 mol% PPh_3, 1 h, RT then *N*-methylmaleimide **319**, 16 h, RT; (iii) 2.0 mol% PPh_3AuNTf_2, EtOH, 16 h, RT.

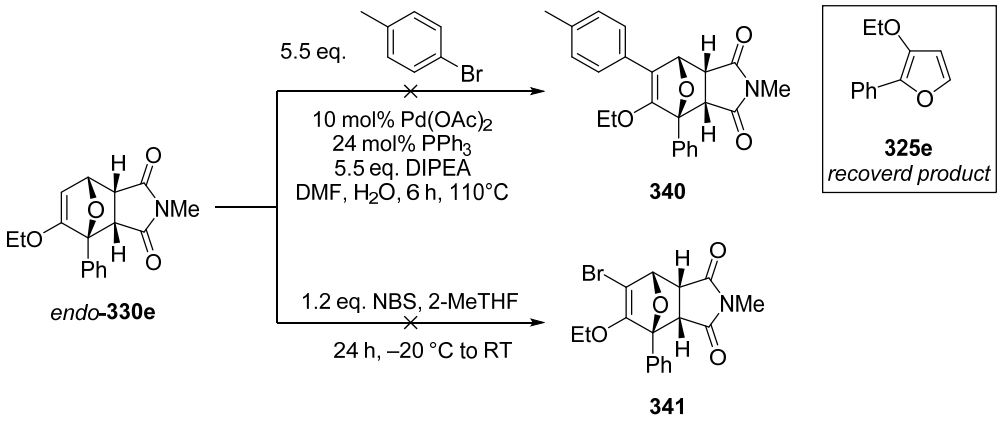
3.2.3. Functional Group Manipulation of Cantharimide Products

Enol ether *endo*-**330e** was readily hydrolyzed by loading the compound onto a Strong Cation eXchange cartridge (SCX-2); a silica column with a bound sulfonic acid residue (**Scheme 68**). Washing the column after 10 minutes with EtOAc gave the corresponding ketone **336** in 80% yield. Ketone **336** was then reduced to the corresponding secondary alcohol **337** using $NaBH_4$ in MeOH, with a 70% isolated yield and complete stereocontrol. Enol ether *endo*-**330e** was also reduced in a diastereoselective manner to give ethyl ether **338** in 76% isolated yield. Treatment of enol ether *endo*-**330e** with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by an oxidative work up gave alcohol **339** in 52% isolated yield with excellent regio- and stereocontrol.



Scheme 68. Transformations of enol ether *endo*-330e. Reagents and conditions: (i) SCX-2; (ii) $NaBH_4$; (iii) H_2, 10% Pd/C; (iv) 9-BBN, then H_2O_2/NaOH.

The transformation of enol ether *endo*-**330e** into cantharimide **340** *via* a Heck arylation was investigated (**Scheme 69**).[195] Treating *endo*-**330e** with 4-bromotoluene in the presence of *N*,*N*-diisopropylethylamine (DIPEA), PPh_3 and $Pd(OAc)_2$ in 85:15 DMF:water and heating the reaction to 110 °C resulted in the formation of furan **325e** rather than cantharimide **340**. This implied that enol ether *endo*-**330e** underwent a retro-cycloaddition reaction at elevated temperatures and that *N*-methylmaleimide **319** was unstable under the reaction conditions. The bromination of enol ether *endo*-**330e** was also explored.[196] However treatment of enol ether *endo*-**330e** with *N*-bromosuccinimide (NBS) in 2-MeTHF resulted in the formation of a complex mixture of products.



Scheme 69. Failed transformations of enol ether *endo*-330e.

3.2.4. Physicochemical Properties

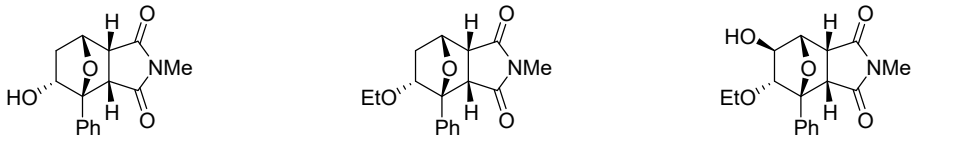
In order for a compound to succeed as a drug it must not only have a high and selective affinity for a target receptor but it must also have appropriate physicochemical properties to ensure favorable absorption and distribution, while minimizing undesired metabolism, elimination and toxicity.[197] Various physicochemical properties are believed to be significant, including lipophilicity,[198] molecular weight (mw)[199] and polar surface area (PSA).[200] It has also been noted that in optimizing the structure of a lead compound into a potential drug candidate that compounds typically become more lipophilic and increase in mw.[201] As such, the physicochemical properties of a lead can have a direct impact on the physicochemical properties of a candidate, and its potential success as a drug. Churcher *et al.* proposed criteria for "Lead-like space", where compounds are typically smaller and more lipophilic than would be typical for a successful drug (**Table 16**).[202] They also emphasized the value of a highly three-dimensional structure, as this is associated with improved solubility, improved receptor affinity and reduced off-target effects.[203]

Table 16. Lead-like properties.[202]

Lead-likeness guide	Preferred values
Lipophilicity guide	$-1 \leq \text{clog}P \leq 3$
Molecular size guide	$14 \leq$ heavy atoms ≤ 26 (mw = 200–350 Da)
Undesired sub-structure filter	• Remove molecules containing chemically reactive, electrophilic or redox active groups. •Favor molecules with lower degrees of aromatic character and/or more 3D shape.

Reproduced from Ref. 202 with permission from John Wiley and Sons.

In order to assess the value of the *endo*-cantharimide products that can be prepared using this methodology to medicinal chemistry, some physicochemical properties of three cantharimides were calculated (**Figure 17**). According to the criteria set down by Churcher *et al.*, the values for clog*P*, mw and polar surface area (PSA) of cantharimides **337**, **338** and **339** fall within the acceptable range of values for "lead-like" compounds. In addition, the structures only contain one aromatic ring and possess a high degree of 3D character. As such, molecules like these could be valuable additions to compound libraries for high throughput screening against biological targets.



337
cLog*P* = 0.46
mw = 273 Da (20 heavy atoms)
PSA = 68 Å^2

338
cLog*P* = 0.98
mw = 301 Da (22 heavy atoms)
PSA = 56 Å^2

339
cLog*P* = 1.20
mw = 317 Da (23 heavy atoms)
PSA = 76 Å^2

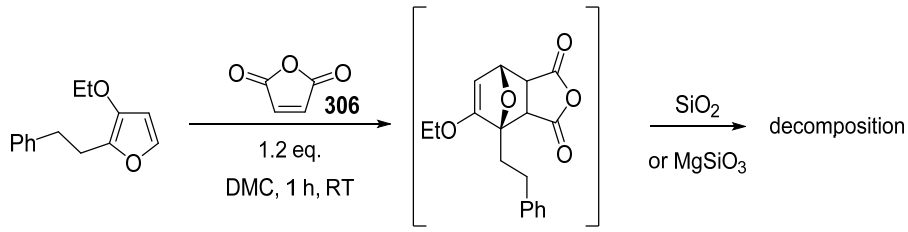
Figure 17. Physicochemical properties of *endo*–cantharimides. Data calculated using ChemDraw 12.

Preliminary biological activity of alcohol **337** and ether **338** was explored using a screen of 40 medicinally important receptors. Unfortunately, this screen did not reveal any significant activity that could be a valuable starting point for further investigations. However, the screen did include the hERG receptor (which is responsible for common toxicity)[204] and no measurable affinity was observed. Finally, the *in vitro* clearance of alcohol **337** in the presence of human microsomes was investigated.[ii] Pleasingly, no turnover was observed below the detectable limit of 0.53 mL min^{-1} g^{-1}.

3.2.5. [4+2]-Cycloadditions with other Dienophiles

[4+2]-Cycloadditions without Lewis Acid Catalysis

Furan **325a** underwent a reaction with 1.2 eq. of maleic anhydride **306** at RT, with 100% conversion of furan **325a** within 1 h (**Scheme 70**). Although analysis of the crude ^{1}H NMR spectrum indicated a product consistent with adduct **342** (*endo*:*exo* = 50:50), attempts to isolate the product by chromatography on silica, using an aminopropyl cartridge or using $MgSiO_3$ failed to give the target compound. It is known that adducts formed from furans and maleic anhydride are more liable to undergo a retro-cycloaddition reaction than the corresponding *N*-methylmaleimide adducts, which may explain the poor stability of adduct **342**.[205]

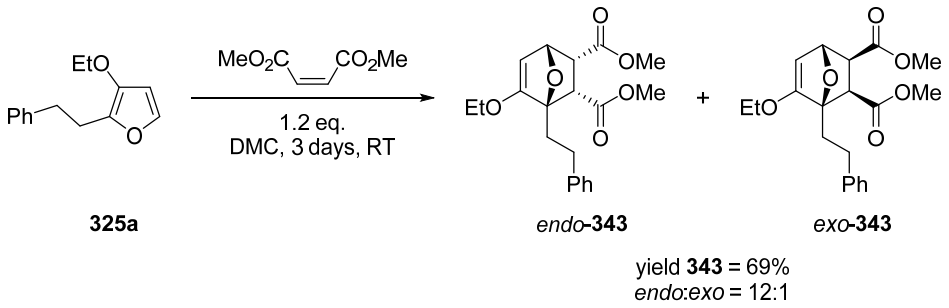


325a **342**

Scheme 70. Reaction of furan 325a with maleic anhydride.

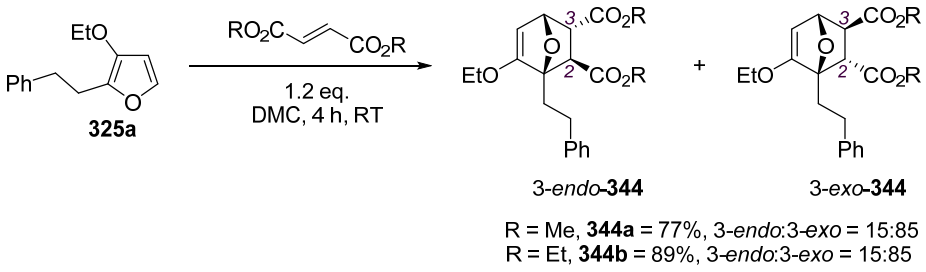
[ii] IVC testing performed by Cyprotex®, 15 Beech Lane, Macclesfield, Cheshire, SK10 2DR, UK.

Treating furan **325a** with 1.2 eq. of dimethyl maleate in DMC resulted in 100% conversion of furan **325a** after 3 days at RT (**Scheme 71**). Enol ether **343** was formed with high *endo*-selectivity (*endo*:*exo* = 12:1), as determined by coupling constant analysis of the crude ^{1}H NMR spectrum. Enol ether **343** was isolated in 69% yield following purification by flash column chromatography.



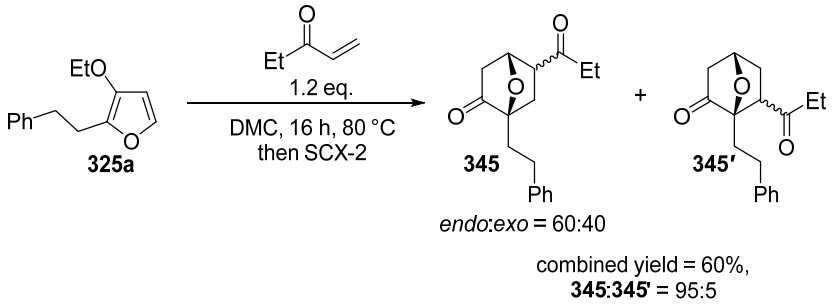
Scheme 71. The reaction of furan 325a with dimethyl maleate.

Both dimethyl and diethyl fumarate reacted readily with furan **325a** at RT to give the corresponding addition products **344**, which were purified by flash column chromatography to give 77% and 89% isolated yields respectively (**Scheme 72**). The diastereoselectivity of the reactions were again determined by coupling constant analysis of ^{1}H NMR spectra and in both cases there was a clear selectivity for the diastereoisomer that is *exo* with respect to the 3-position (3-*exo*-**344**). The reaction of a fumarate with a substituted furan was without literature precedent.



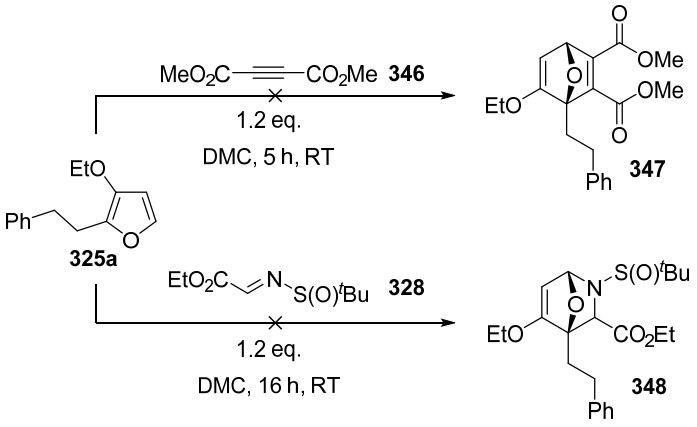
Scheme 72. Reaction of furan 325a with dimethyl and diethyl fumarates.

Furan **325a** underwent a slow reaction with ethyl vinyl ketone at RT, but at 80 °C the reaction reached completion within 16 h (**Scheme 73**). The direct cycloaddition product proved to be relatively unstable, but hydrolysis of the enol ether gave the corresponding ketone that was readily purified. Analysis of the crude ^{1}H NMR spectrum indicated the presence of two regioisomers **345** and **345'** in the ratio 95:5. The major regioisomers **345** was formed as 60:40 mixture of *endo*- and *exo*-diastereoisomers. Following column chromatography ketones **345** and **345'** were isolated in a combined yield of 60%.



Scheme 73. [4+2]-Cycloaddition of furan 325a with ethyl vinyl ketone.

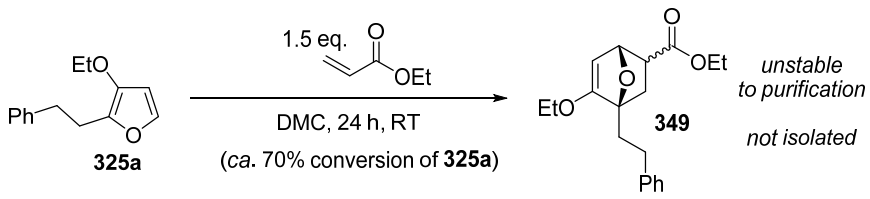
Furan **325a** also reacted with dimethyl acetylenedicarboxylate **346**, with 100% conversion of the furan observed after 5 h at RT (**Scheme 74**). However, analysis of the crude ^{1}H NMR spectrum showed that the product was a complex mixture of products with no clear evidence for the expected adduct **347**. A possible explanation was that the cycloaddition reaction occurred but that the immediate product was unstable and decomposed under the reaction conditions. The reaction of furan **325a** with imide **328** proceeded in a similar manner; again the furan was consumed but only a complex mixture of unidentified products was isolated from the reaction.



Scheme 74. Failed cycloaddition reactions with furan 325a.

Lewis-Acid Catalyzed [4+2]-Cycloadditions

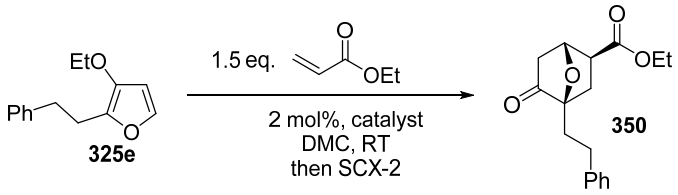
The reaction of furan **325a** and ethyl acrylate was investigated under the standard reaction conditions but was found to proceed slowly at RT, with *ca.* 70% conversion of furan **325a** observed after 24 h (**Scheme 75**). In light of this, the possibility of accelerating the reaction through use of a Lewis acid catalyst was investigated. It was found that enol ether **349** was unstable to purification by flash silica gel chromatography so it was not possible to isolate this compound.



Scheme 75. [4+2]-Cycloaddition of furan 325a and ethyl acrylate.

The reaction of furan **325a** and 1.5 eq. of ethyl acrylate was explored at RT with a series of Lewis acids, with the results given in **Table 17**. Given the difficulty in isolating enol ether **349**, the crude reaction mixtures were filtered through a SCX-2 plug to hydrolyze the cycloaddition product and form ketone **350**. Both $Yb(OTf)_3$ and $HfCl_4$ were effective catalysts for the cycloaddition, with 100% conversion of furan **325a** observed after 3 h and 6 h respectively (Entries 1 and 2). In contrast BF_3.THF and $Cu(OTf)_2$ were not effective catalysts for this transformation, with less than 100% conversion observed after 8 h (Entries 3 and 4). While $Yb(OTf)_3$ gave the shortest reaction time, $HfCl_4$ gave the best yield and, using 2.0 mol% $HfCl_4$ as catalyst, ketone **350** was isolated in 89% yield as a 65:35 mixture of *endo*- and *exo*-diastereoisomers (Entry 2).

Table 17. Catalyst screen for that reaction of furan 325a and ethyl acrylate.

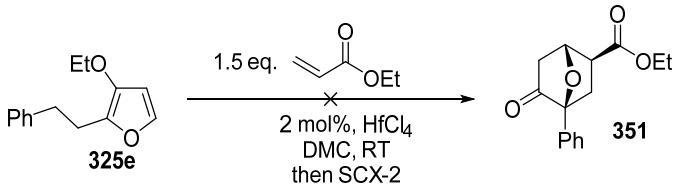


Entry	Catalyst	Time/h	Yield **350**/%[a]	*endo*:*exo*[a]
1	$Yb(OTf)_3$	3	70	65:35
2	$HfCl_4$	6	90 (89)[b]	65:35
3	$Cu(OTf)_2$	8[c]	30	85:15
4	BF_3.THF	8[c]	30	85:15

[a] As determined from a ^{1}H NMR spectrum of the crude product (using C_6HCl_5 as an internal standard). [b] Isolated yield; [c] Furan **325e** still present.

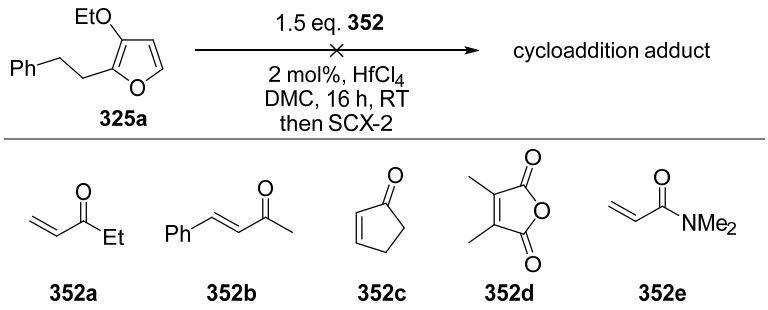
Unfortunately, the substrate scope with regard to the furan was limited. Treating 2-Ph furan **325e** with ethyl acrylate under the optimized conditions resulted in little conversion of the furan and no formation of the target product **351** (**Scheme 76**). A screen of alternative catalysts in DMC [$Hf(OTf)_4$, $Yb(OTf)_3$, $Sc(OTf)_3$, $La(OTf)_3$] did not yield any evidence for the formation of a cycloaddition product either. Finally the reaction was attempted under thermal conditions by heating the furan with 2.0 eq. of ethyl acrylate

without solvent at 100 °C for 16 h, but no ketone **351** was formed as judged by analysis of the ^{1}H NMR spectrum.



Scheme 76. Failed reaction of furan 325e and ethyl acrylate.

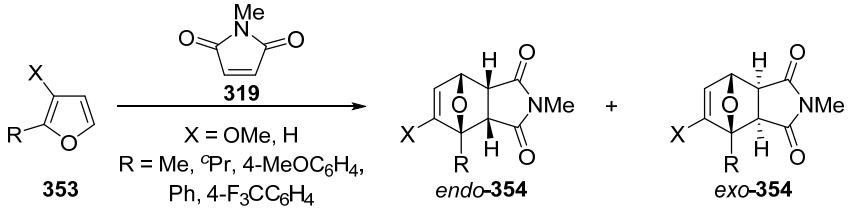
The dienophile scope was also evaluated. Unfortunately, none of the dienophiles in **Scheme 77** underwent reaction with furan **325a** to form a cycloaddition product that could be isolated. For enones **352a** and **352b**, 100% conversion of furan **325a** was observed within 16 h but analysis of the crude ^{1}H NMR spectrum revealed a complex mixture of products. For the case of cyclopentenone **352c**, anhydride **352d** and acrylamide **352e**, no significant reaction was observed.



Scheme 77. Dienophiles that failed to cyclize with furan 325a.

3.2.6. Effect of a 3-Alkoxygroup on the [4+2]-Cycloaddition of Furans and *N*-Methylmaleimide: A Computational Study

The aim of this computational study was to quantify the thermodynamic and kinetic effect of a 3-alkoxy group on the [4+2]-cycloaddition of 2-substiuted furans with *N*-methylmaleimide **319**. The reaction of ten furans **353** with *N*-methylmaleimide **319** were modelled using Gaussian09[206] (**Scheme 78**). A 3-methoxy group was selected over a 3-ethoxy group in order to simplify structure optimizations.



Scheme 78. Model reactions for the computational study.

Structure Optimization

Before any reactions could be investigated it was first necessary to find the lowest energy conformation of starting materials and products. This was done using the M06-2X/6-31G(d) level of theory, which was chosen after preliminary calculations showed that it was able to reproduce reported calculated energies for related furans, dienophiles and adducts that had been published by Svatoš *et al*.[182] The first question that was addressed was the favored rotamer of 3-methoxyfurans. It was energetically more favorable for the methoxy group of a 3-methoxyfuran to point away from the adjacent substituent at the 2-postion. For example, furan **353a** was 13.3 kJ mol^{-1} more stable than rotamer **353a'** (**Figure 18**). A similar effect was observed in the cantharimide products. For example, *endo*-**354a** was 11.6 kJ mol^{-1} more stable than the corresponding rotamer *endo*-**354a'**.

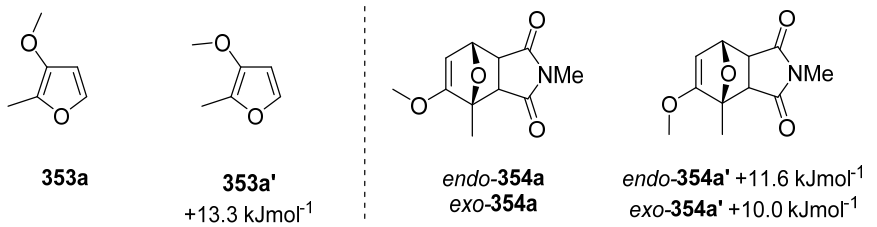
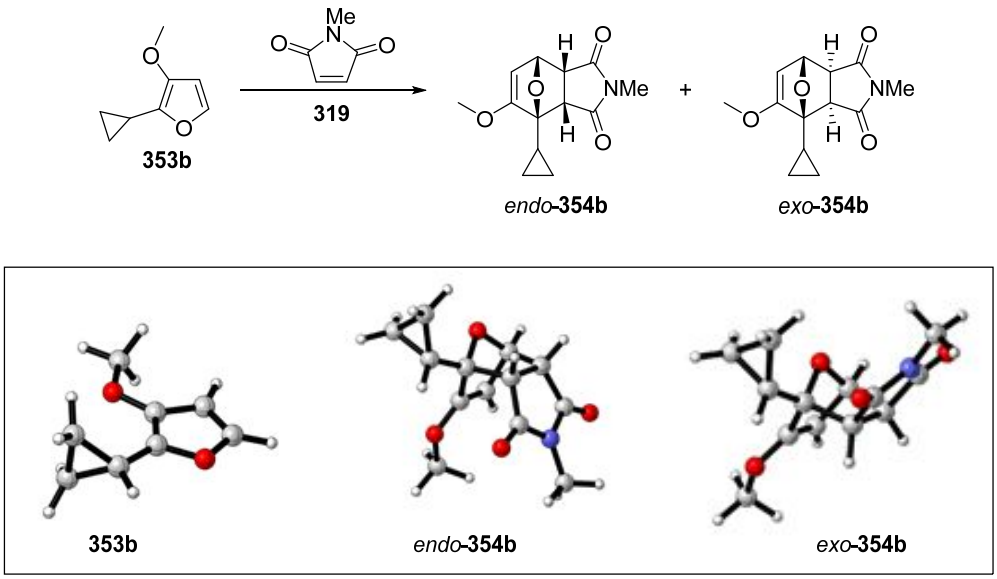


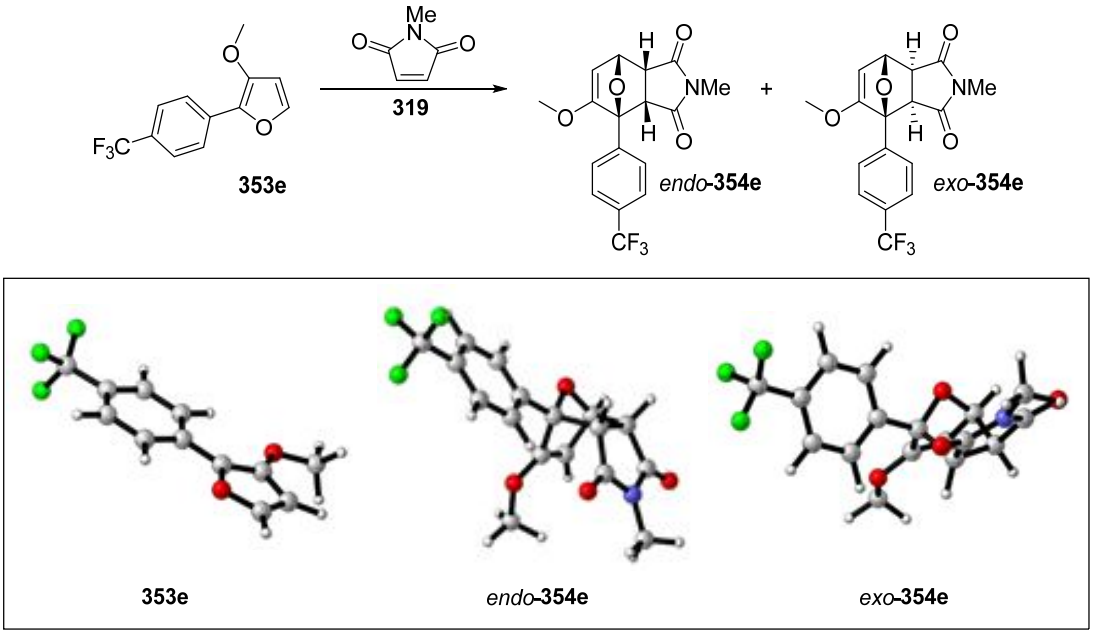
Figure 18. Rotation about the C-OMe bond.

Examining the geometries of 2-cyclopropylfuran **353b** and cantharimides **354b** revealed three rotamers for each compound (**Scheme 79**). For these examples, the lowest energy conformation for the starting material and product were used to calculate ΔH and ΔG, but all rotamers were considered to calculate minimum transition state geometries. Then the lowest energy transition state was used to calculate $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$. The same approach was used for the corresponding 3-H furan.



Scheme 79. Energy and frequency minimized geometries for furan 353b and cantharimides 354b.

In contrast, where the 2-substituent was an aromatic ring there was a strong preference for a single conformation in both starting material and adduct. For the 2-aryl furans the two rings preferred to sit coplanar. For the cantharimides the preferred geometry saw the aromatic ring approximately coplanar with the ether bridge. The dihedral angle across the rotatable C-C bond for each isomer changed little as the aromatic ring was varied. The optimized geometries for furan **353e** and cantharimides **354e** are illustrated in **Scheme 80**.

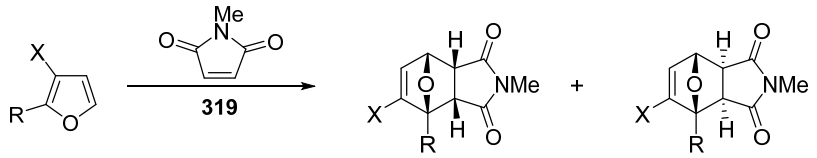


Scheme 80. Energy and frequency minimized geometries for furan 353e and cantharimides 354e.

Free Energy and Enthalpy Calculation

By calculating minimum gas-phase energies for starting materials, cantharimides and transition states it was possible to calculate values for ΔH or $\Delta H^{\ddagger}$, ΔG and $\Delta G^{\ddagger}$ for each reaction, with the results given in **Table 18**. Transition state searches were conducted using the QST2 method at the M06-2X/6-31G(d) level of theory. The calculations were also performed for reactions in a series of solvents (hexane, Et_2O, CH_2Cl_2, PhMe, EtOH, MeCN and water), but this had little effect on ΔH or $\Delta H^{\ddagger}$, ΔG or $\Delta G^{\ddagger}$. Performing calculations in DMC was considered but this solvent was not an available option in Gaussian09 and so was thus not trivial to model.

Table 18. Calculated reaction and transition state enthalpies and free energies for the formation of cantharimides 354.[a]

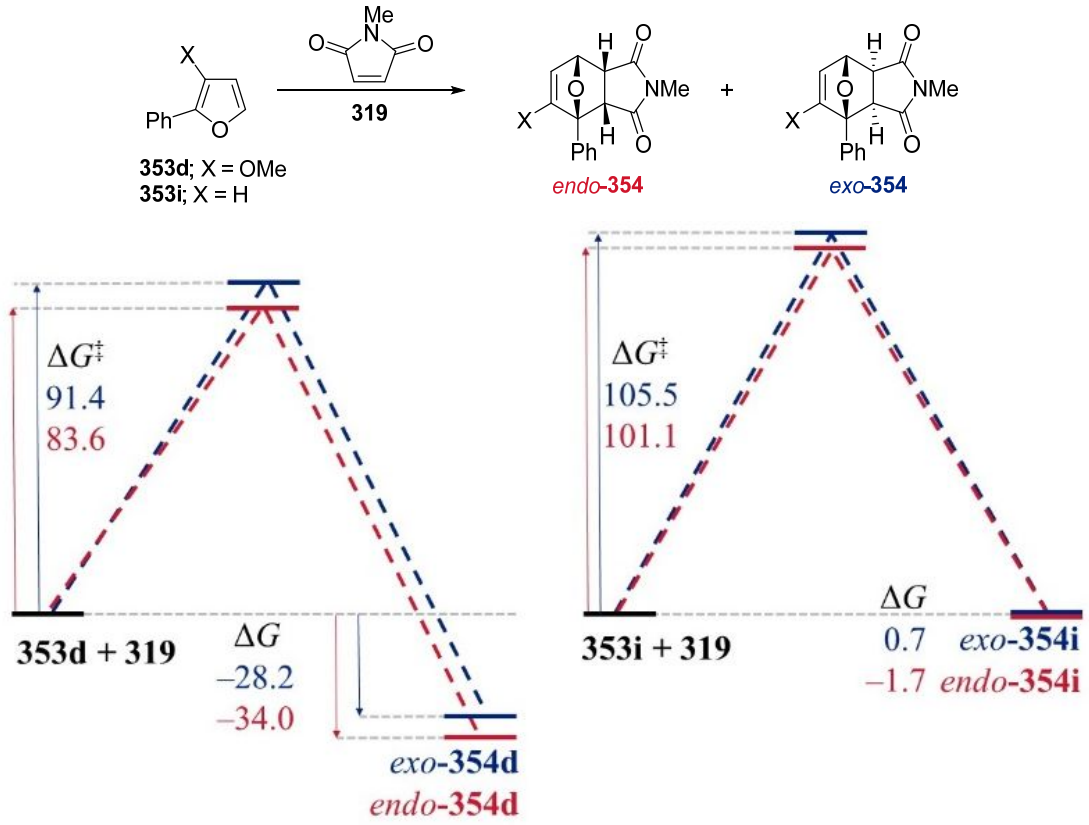


R	X	Product	ΔH	$\Delta H^{‡}$	ΔG	$\Delta G^{‡}$
Me	OMe	*endo*-**354a**	–106.4	18.8	–41.5	81.1
Me	OMe	*exo*-**354a**	–112.8	23.2	–47.7	82.1
^{c}Pr	OMe	*endo*-**354b**	–109.4	11.6	–44.1	75.0
^{c}Pr	OMe	*exo*-**354b**	–116.5	18.7	–53.2	78.6
4-$MeOC_6H_4$	OMe	*endo*-**354c**	–90.2	22.3	–32.5	76.8
4-$MeOC_6H_4$	OMe	*exo*-**354c**	–88.6	32.6	–30.1	85.3
Ph	OMe	*endo*-**354d**	–88.4	25.3	–34.0	83.6
Ph	OMe	*exo*-**354d**	–87.3	35.4	–28.2	91.3
4-$F_3CC_6H_4$	OMe	*endo*-**354e**	–89.2	28.2	–25.3	85.9
4-$F_3CC_6H_4$	OMe	*exo*-**354e**	–87.9	39.0	–23.8	96.8
Me	H	*endo*-**354f**	–73.1	40.5	–11.8	97.9
Me	H	*exo*-**354f**	–82.3	41.3	–16.8	96.2
^{c}Pr	H	*endo*-**354g**	–72.3	40.1	–12.5	92.2
^{c}Pr	H	*exo*-**354g**	–79.3	43.1	–10.3	92.8
4-$MeOC_6H_4$	H	*endo*-**354h**	–59.8	44.1	–6.1	95.4
4-$MeOC_6H_4$	H	*exo*-**354h**	–58.7	48.9	–3.6	98.8
Ph	H	*endo*-**354i**	–61.5	43.1	–1.7	101.1
Ph	H	*exo*-**354i**	–60.0	48.8	0.7	105.5
4-$F_3CC_6H_4$	H	*endo*-**354j**	–60.6	45.7	–0.9	101.6
4-$F_3CC_6H_4$	H	*exo*-**354j**	–60.3	51.9	0.9	108.3

[a]All values are in kJ mol^{-1}. All data is calculated for species in the gas phase. The optimized geometries of all compounds and transition states can be found in appendix to this thesis.

Analysis of the data in **Table 18** showed that the 3-alkoxy group has a dramatic impact on the thermodynamic driving force of the furan-Diels–Alder reaction. The introduction of a methoxy group at the designated position decreases the Gibbs free energy of reaction (ΔG) by 24–34 kJ mol^{-1}. This impact is most significant where the substituent is aromatic,

for example the 2-Ph furans illustrated in **Scheme 81**. For 2-phenylfuran **353i** the reaction to form the thermodynamically more stable adduct *endo*-**354i** has a value of ΔG = –1.7 kJ mol^{-1}. Such a low thermodynamic driving force is not practical for an efficient synthesis of cantharimide **354i**. By comparison, the reaction of 3-methoxyfuran **353d** and *N*-methylmaleimide **319** has a significant thermodynamic driving force, which is consistent with kinetic control (ΔG_{exo} = –28.2 kJ mol^{-1} and ΔG_{endo} = –34.0 kJ mol^{-1}). As would be expected for an electron rich diene,[207] the 3-methyoxy group also reduces the kinetic barrier for the Diels–Alder reaction. However, this effect was less pronounced, with a difference of 11–23 kJ mol^{-1}.



Scheme 81. Reaction and activation free energies for the [4+2]-cycloadditions of 2-phenylfurans and *N*-methylmaleimide 319. All values are in kJ mol^{-1}.

Transition State Geometries

The energy minimized structures for the *endo*- and *exo*-transition states for the formation of cantharimides **354d** are shown in **Figure 19**. It is notable that in both cases the transition state geometries of the furan and maleimide components are relatively flat, as would be expected for an early transition state. The transition state geometries are also relatively symmetrical, with little difference in the length of the forming bonds.

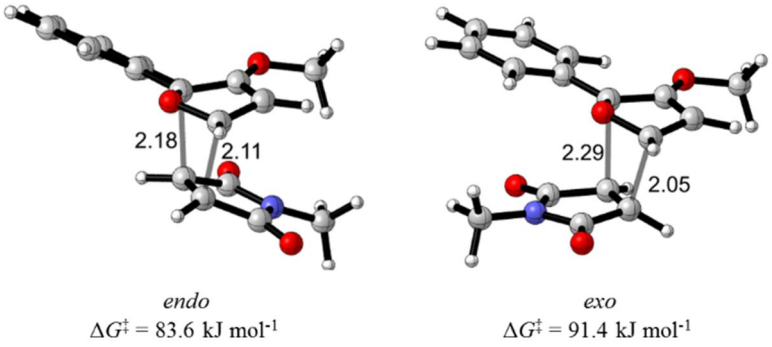
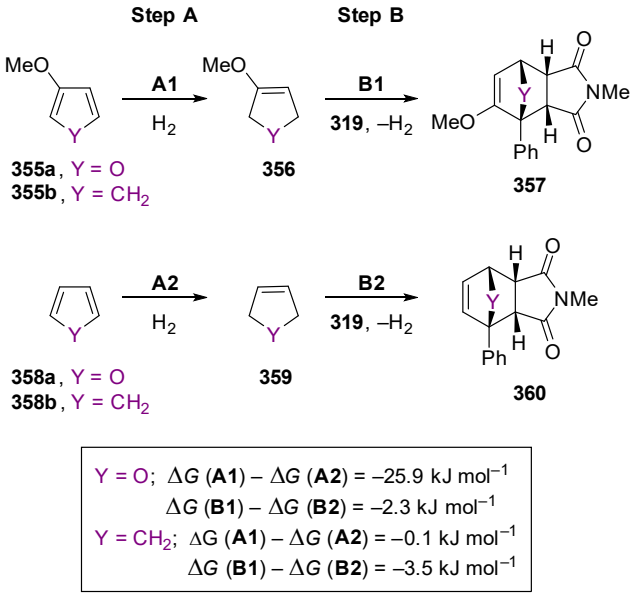


Figure 19. Transition states for *endo*- and *exo*-cantharimides 354d.

Hydrogenation Thermodynamic Cycle

The reversibility of Diels–Alder reactions where the diene is a furan has been attributed to the loss of aromatic stabilization upon formation of the adduct, resulting in a facile retro-cycloaddition.[182] In order to examine the effect of a 3-methoxy group on this phenomenon, thermodynamic cycles involving the partial hydrogenation of 3-methoxyfuran **355a** and furan **358a** to the corresponding 2,5-dihydrofurans **356a** and **359a** were considered (**Scheme 82**). It is notable that the free energy of hydrogenation for furan **355a** is 25.9 kJ mol^{-1} greater than for 3-methoxyfuran **358a**. For the second step in the cycle to form adducts **357** and **360** no significant difference in ΔG was observed. In contrast, the analogous thermodynamic cycles for the corresponding cyclopentadienes **355b** and **358b** revealed little difference in ΔG for either Step A or Step B.



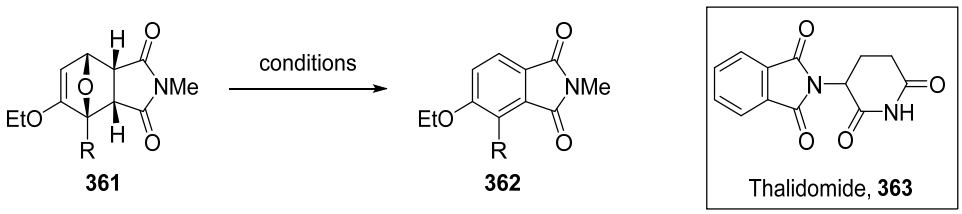
Scheme 82. Hydrogenation Study.

The observation that the addition of a methoxy group had little impact on ΔG for step B suggested that the formation of the two C-C bonds was not the determining factor in

explaining the difference in ΔG for the reactions of furan and 3-methoxyfuran with *N*-methylmaleimide. Rather this could be attributed to the change in conjugation associated with the cycloaddition reaction. These results suggest that the 3-methoxy group reduced the thermodynamic penalty associated with the loss of conjugation upon partial hydrogenation to the 2,5-dihydrofuran. The fact that a similar effect is not observed with the corresponding cyclopentadienes suggested that loss of aromaticity is the significant factor. In other words, a 3-methoxy group can reduce the energetic cost of losing aromaticity upon the cycloaddition of a furan with *N*-methylmaleimide.

3.2.7. Aromatization of Cantharimide Products

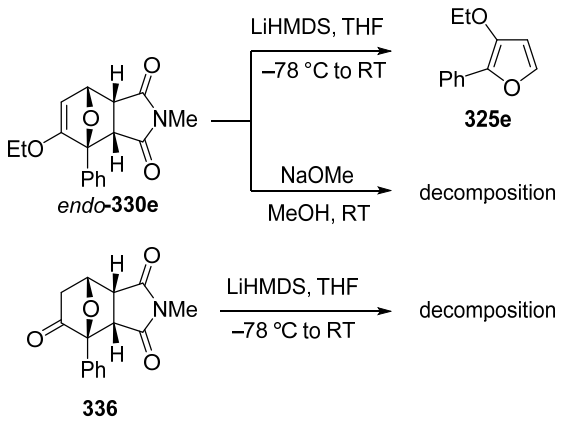
The dehydration of 7-oxabicyclo[2.2.1]heptanes under acidic or basic conditions was identified as a potentially valuable route to highly-substituted aromatic compounds, such as phthalimides **362** (**Scheme 83**). In principle, this could be conducted using a mixture of *endo*- and *exo*-diastereoisomers as both would converge to the same product. Phthalimide is a privileged scaffold for drug discovery and forms the core of a number of existing and potential therapies.[208] Many of these are derivatives of Thalidomide **363**, which is currently used in the treatment of multiple myeloma.[209]



Scheme 83. Proposed aromatization of cantharimides 361.

Base-Mediated Ring-Opening.

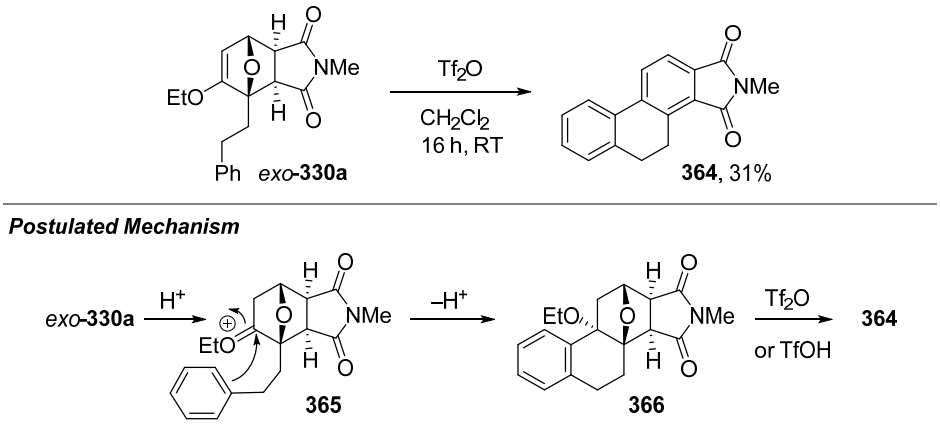
There is reasonable precedent for the aromatization of ether-bridged [4+2]-cycloaddition products using strong bases (**Scheme 84**).[210] However, treating cantharimide *endo*-**330e** with lithium hexamethyldisilazide (LiHMDS) in anhydrous THF at –78 °C did not result in any evidence for cleavage of the ether bridge or formation of a phthalimide product. In addition to recovered starting material, 3-alkoxyfuran **325e** was observed in the crude ^{1}H NMR spectrum. This suggested that the reaction conditions induced a retro-[4+2]-cycloaddition of cantharimide *endo*-**330e**. No such reaction was observed when cantharimide *endo*-**330e** was treated with NaOMe in MeOH, but this only resulted in significant decomposition. Ketone **336** was also treated with LiHMDS in an attempt at inducing aromatization, but this too resulted in significant decomposition.



Scheme 84. Reaction of enol-ether *endo*-330e and ketone 336 with LiHMDS.

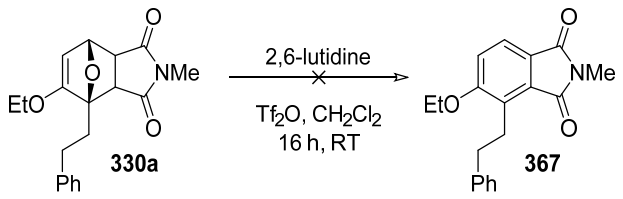
Tf_2O-Mediated Ring-Opening

The possibility of cleaving the ether bridge using Tf_2O was briefly considered. It was found that treating enol-ether *exo*-**330a** with Tf_2O in anhydrous CH_2Cl_2 gave a complex mixture of products. Following purification by flash column chromatography phthalimide **364** was isolated in 31% yield (**Scheme 85**). It was postulated that the formation of phthalimide **364** proceed through an acid-mediated electrophilic aromatic substitution of the pendent phenyl group, followed by aromatization of the resulting 7-oxabicyclo[2.2.1]heptane **366**.



Scheme 85. Synthesis of phthalimide 364 from enol ether *exo*-330a.

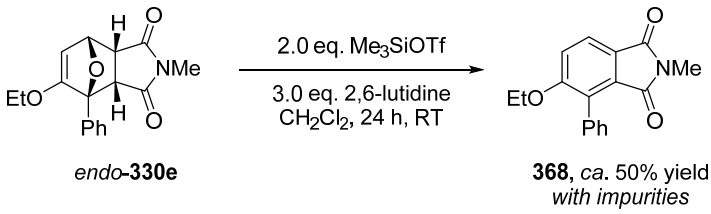
In an attempt to convert cantharimide **330a** into phenol ether **367**, cantharimide **330a** was treated with Tf_2O in the presence of 2,6-lutidine (**Scheme 86**). However, no reaction was observed and cantharimide **330a** was recovered from the reaction. An interpretation of this result is that it was TfOH rather that Tf_2O that was responsible for the aromatization of intermediate cantharimide **366** in the formation of phthalimide **364** (**Scheme 85**).



Scheme 86. Failed aromatization of cantharimide 330a under basic conditions.

Me_3SiOTf-Mediated Aromatization

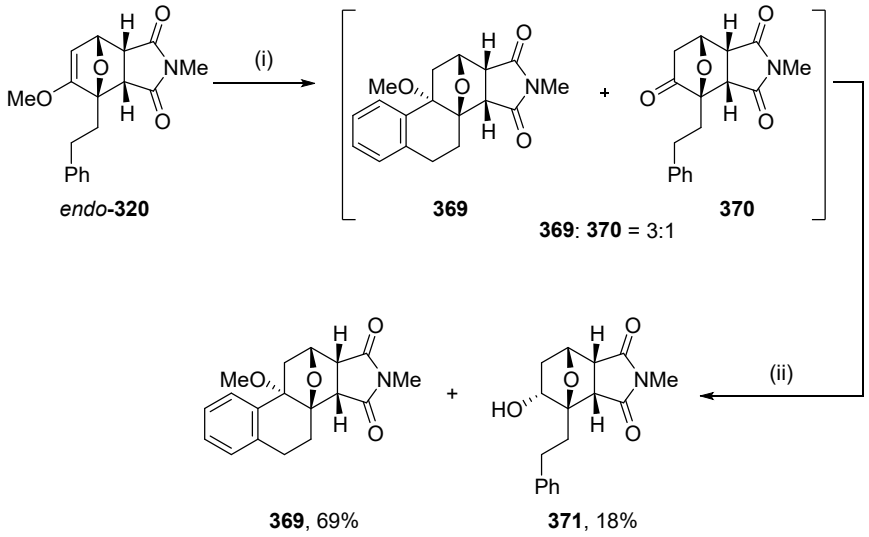
The aromatization of enol ether *endo*-**330e** was considered under basic conditions using Me_3SiOTf as a dehydrating agent.[211] After 24 h a 3:1 mixture of phthalimide **368** and starting material *endo*-**330e** were isolated. However, column chromatography failed to generate phthalimide **368** in sufficiently high purity and the yield was estimated at 50% (**Scheme 87**). Heating the reaction at reflux for 24 h resulted in 100% conversion of cantharimide *endo*-**330e** and approximately 40% yield of phthalimide **368**, but again purification by silica gel column chromatography gave phthalimide **368** in only modest purity. Given the challenge of purifying this reaction, these conditions were not pursued further.



Scheme 87. Aromatization of adduct *endo*-330e using Me_3SiOTf.

Acid-Mediated Ring-Opening

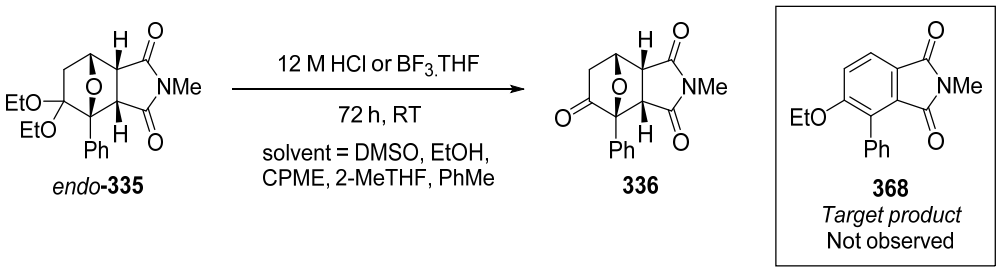
As an initial study, a solution of cantharimide *endo*-**320** in CH_2Cl_2 was treated with TFA at RT (**Scheme 88**). This did not result in any formation of an aromatized product; rather ether **369** and ketone **370** were formed in the ratio 3:1. These two products were inseparable by silica gel chromatography so the mixture was treated with $NaBH_4$ in MeOH to give a separable mixture of ether **369** and alcohol **371**. After purification, ether **369** was isolated in 69%.



Scheme 88. Acid-catalyzed rearrangement of cantharimide *endo*-320. Reagents and conditions: (i) TFA, CH_2Cl_2; (ii) $NaBH_4$, MeOH.

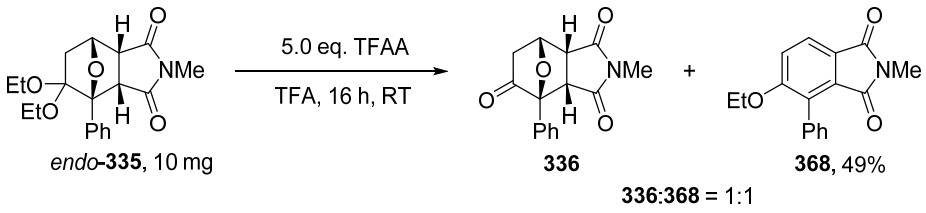
It was unclear whether ketone **370** was formed under the reaction conditions or whether it was only formed on work up. Repeating the reaction using anhydrous conditions and leaving the reaction for a further 8 h resulted in the same 3:1 mixture of products. A possible solution was to add $HC(OMe)_3$ to the reaction to regenerate starting material *endo*-**320** from any ketone **370** formed in the reaction. However, after a 24 h reaction only ketone **370** was present in the crude product.

Given the complication of a pendent aromatic group and the apparent sensitivity of enol ethers to acidic conditions, diethyl acetal **335** was identified as a suitable substrate for investigating acid-mediated ring-opening (**Scheme 89**). Five different solvents were screened for the acid-mediated aromatization of acetal **335** using both 12 M aq. HCl and BF_3.THF as a potential catalyst. Acetal **335** was stirred in a 10:1 mixture of solvent:acid for 3 days at RT, but in all ten experiments no evidence of aromatization was observed. The only product formed in this solvent screen was the hydrolyzed product **336**.



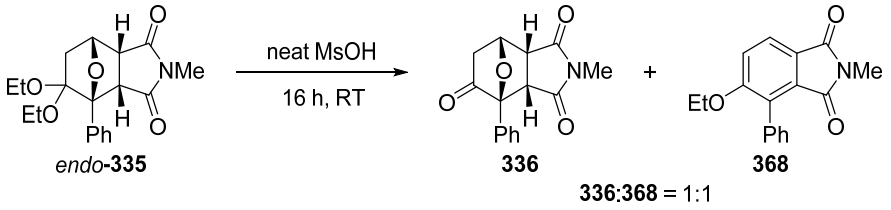
Scheme 89. Solvent screen for the acid-mediated rearrangement of acetal *endo*-335.

Given the difficulty in aromatizing acetal **335**, more forcing acidic conditions were investigated. Stirring acetal *endo*-**335** in neat TFA with 5.0 eq. of TFAA as a dehydrating agent at RT gave phthalimide **368** in 49% yield on a 10 mg scale (**Scheme 90**). Analysis of the crude ^{1}H NMR spectrum suggested that phthalimide **368** was formed alongside ketone **336** in a 1:1 ratio.



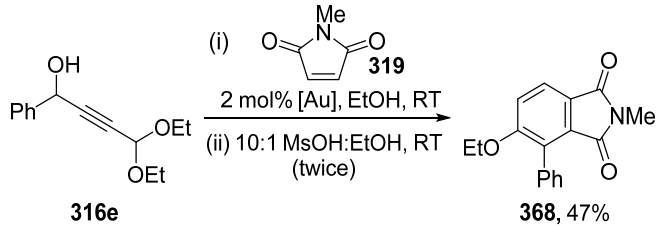
Scheme 90. TFA-mediate aromatization of acetal *endo*-335.

This result suggested that the key to optimizing the aromatization reaction was reducing the rate of hydrolysis relative to that of aromatization. Given that forcing acidic conditions appeared to be beneficial, acetal *endo*-**335** was stirred in MsOH at RT for 16 h. (**Scheme 91**). Pleasingly this resulted in formation of phthalimide **368** without the need for an additional dehydrating agent. However, these conditions offered no advantage in terms on minimizing the formation of ketone **336**.



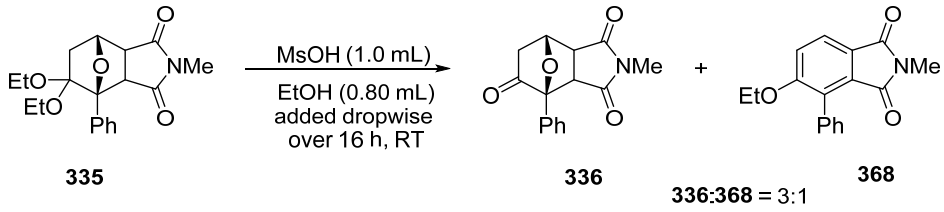
Scheme 91. Acid-mediated aromatization of acetal *endo*-335 using MsOH.

An attempt was made to convert propargylic alcohol **316e** into phthalimide **368** without isolation of the cantharimide intermediates (**Scheme 92**). Alcohol **316e** was converted to the corresponding cantharimide *endo*-**335** using 2.0 mol% PPh_3AuNTf_2 and *N*-methylmaleimide **319** (**Section 4.2.2., Scheme 67**). This material was then concentrated and treated with MsOH along with 10% EtOH by volume, which was added in an attempt to minimize the formation of ketone **336**. After 16 h the reaction was worked-up and the crude product again treated with MsOH and EtOH (10:1) in order to convert remaining ketone **336** into phthalimide **368**. After this additional step phthalimide **368** was isolated in 47% yield from propargylic alcohol **316e**.



Scheme 92. One-pot synthesis of phthalimide 368 from alcohol 316a.

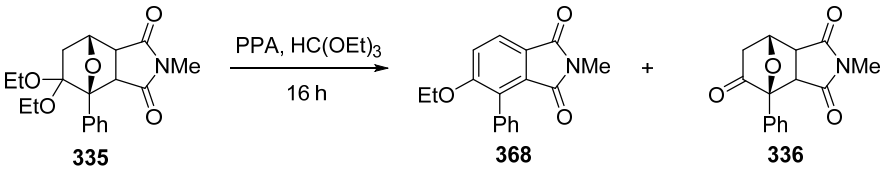
A key limitation of MsOH as a reagent for the aromatization of cantharimides is the hydrolysis of diethylacetal **335** to the corresponding ketone **336**. Adding EtOH to the reaction mixture had a limited effect at reducing this hydrolysis because of the autocatalytic reaction of EtOH and MsOH to form MsOEt. This was confirmed by treating MsOH with EtOH in the ratio 10:1; after 1 h analysis of the reaction by ^{1}H NMR spectroscopy clearly showed that all the EtOH had been converted to MsOEt. A possible solution was to treat acetal **335** with MsOH and then add EtOH dropwise to the reaction mixture (**Scheme 93**). However, this proved to be detrimental to the reaction, with a reduced level of phthalimide **368** formed.



Scheme 93. Aromatization reaction of acetal 335 using MsOH and a dropwise addition of EtOH.

Given the problems associated with the aromatization of acetal **335** in MsOH, alternative catalysts were considered. Using AcOH, PTSA.H_2O, sulfuric acid and hydrochloric acid in combination with a $HC(OEt)_3$ dehydrating agent did not result in aromatization of acetal **335**. Polyphosphoric acid (PPA) was considered as an aromatization agent, with the results summarized in **Table 19**.

Table 19. Attempts to aromatize acetal 335 using polyphosphoric acid (PPA).

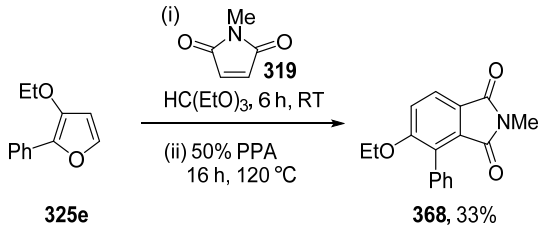


Entry	Ratio PPA: $HC(OEt)_3$	Temperature/°C	**368:336**/%[a]
1	10:1	RT	1:4
2	10:1	100	decomposition
3	1:1	100	1:4
4	1:1	120	3:2
5	1:1	150	3:1
6[b]	1:1	150	3:1[c]

[a] Determined from the ^{1}H NMR spectrum of the crude product. [b] Reaction heated for 24 h. [c] Phthalimide **368** isolated in 42% yield.

Stirring acetal **335** in a 10:1 mixture of polyphosphoric acid (PPA) and $HC(OEt)_3$ resulted in the formation of phthalimide **368** alongside ketone **336** in the ratio 1:4 (**Table 19**, Entry 1). Increasing the reaction temperature to 100 °C resulted in decomposition (Entry 2), however when the proportion of PPA used was decreased it was again possible to isolate phthalimide **368** alongside ketone **336** (Entry 3). Increasing the reaction temperature increased the ratio of phthalimide **368** to ketone **336** (Entries 4 and 5), with a 150 °C reaction temperature giving a ratio of 3:1. However, a longer reaction time of 24 h did not improve this ratio (Entry 6). Purification of this reaction gave phthalimide **368** in 42% isolated yield.

A one-pot synthesis of phthalimide **368** over two steps from furan **325e** was attempted (**Scheme 94**). Furan **325e** was treated with *N*-methylmaleimide **319** in $HC(OEt)_3$ and the reaction stirred at RT. After 6 h the reaction was treated with PPA and the resulting solution heated at 120 °C for 16 h. Following purification, phthalimide **368** was isolated in 33% yield.



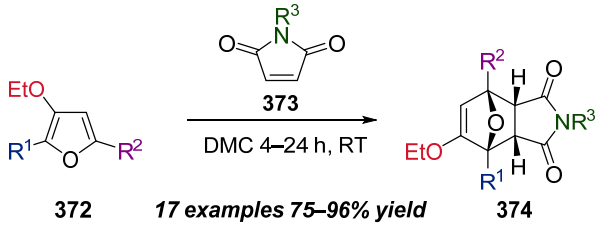
Scheme 94. One-pot synthesis of phthalimide 368 from furan 325a.

Aromatization Conclusion

In conclusion, phthalimide **368** was prepared from the corresponding cantharimide under a variety of reaction conditions. However, the conditions required to achieve the aromatization reaction were always forcing and the best isolated yields were relatively low. While this route offers an interesting new approach into highly substituted phthalimides it was not pursued further due to these two limitations.

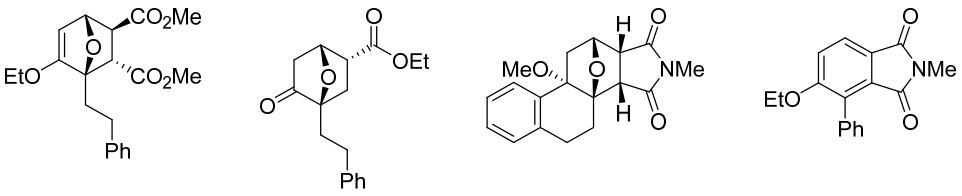
3.3. Chapter III Summary

Highly substituted *endo*-cantharimides **374** were prepared *via* the [4+2]-cycloaddition of 3-alkoxyfurans and maleimides under environmentally benign conditions (**Scheme 95**). The reaction was effective with a variety of 3-alkoxyfurans, including those bearing aromatic and heteroaromatic groups at the 2-position, giving cantharimide products in good yield and with reasonable *endo*-control. The reaction was also effective with a number of *N*-substituted maleimides, allowing cantharimides to be prepared in a highly convergent fashion. It was shown that the enol ethers formed by this approach could be efficiently converted into a number of *endo*-cantharimide products with promising lead-like properties. In addition, computational calculations were performed to quantify the effect that a 3-alkoxy group had on the thermodynamics and kinetics of furan-Diels–Alder reactions.



Scheme 95. Summary of *endo*-cantharimide synthesis.

In addition to cantharimide products, the methodology was extended to synthesize a variety of novel heterocycles from other dienophiles (**Scheme 96**). Finally, acid-mediated rearrangements of cantharimide products were used to make extended ring system **369** and phthalimide **368**.



3-*exo*-**346a** *endo*-**352** **369** **368**

Scheme 96. Novel heterocycles prepared from 3-alkoxyfurans.

Chapter IV. Synthesis of Chiral THFs *via* the Dehydration of Pentoses

4.1. Introduction

4.1.1. The Application of THFs in Medicinal Chemistry

Nucleoside analogues are an important class of compounds in medicinal chemistry, which have been widely developed as antiviral agents, antibiotics and antitumor agents.[212] Compounds of this class mimic the tetrahydrofuran (THF) ring of nucleosides and typically possess a nucleobase at the α-position (**Figure 20**). Examples include the chemotherapy agent Cytarabine **401**,[213] reverse transcriptase inhibitor Zalcitabine **402**[214] and antiretroviral drug Azidothymidine (AZT) **403**.[215]

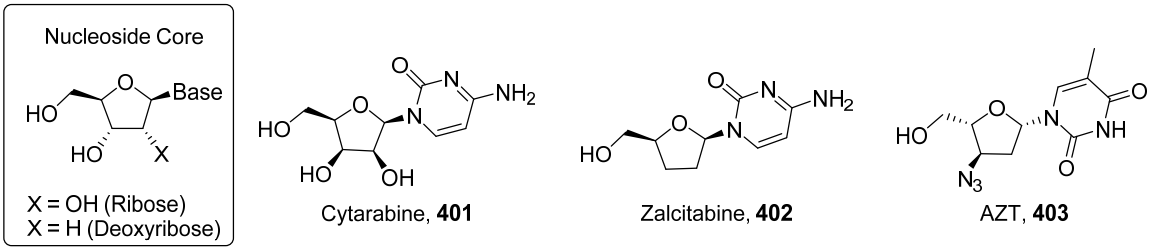


Figure 20. Nucleoside analogues in medicinal chemistry.

A structurally related class of drugs are based on a saturated THF scaffold, with examples illustrated in **Figure 21**. Alfuzosin **404** and structurally related Terazosin **405** are both α-1 antagonists and are used in the treatment of benign prostatic hyperplasia.[216, 217] Fosamprenavir **406a** (a prodrug of protease inhibitor Amprenavir **406b**) is used in the treatment of HIV.[218] Naftidrofuryl **407** is a vasodilator and a treatment for cerebral vascular disorders[219] while Mefruside **408** is a diuretic used for the treatment of edema.[220]

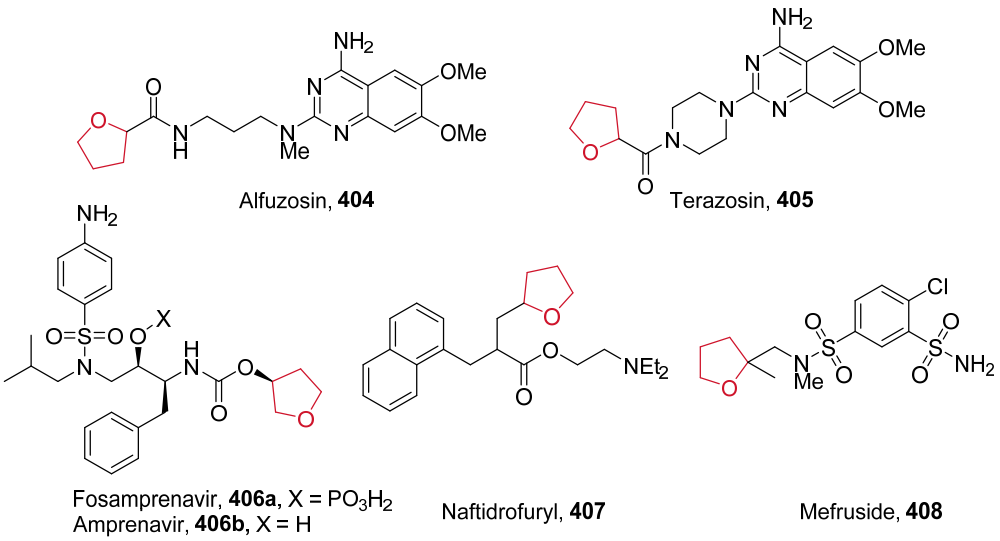


Figure 21. Clinical drugs containing a THF.

A valuable drug bearing a fused bis-THF core is isosorbide **409**, which is used as a diuretic to treat hydrocephalus (**Figure 22**). However, isosorbide has also been used more widely in drug development as a scaffold.[221] Both isosorbide mononitrate **410** and isosorbide dinitrate **411** are used as vasodilators to treat angina.

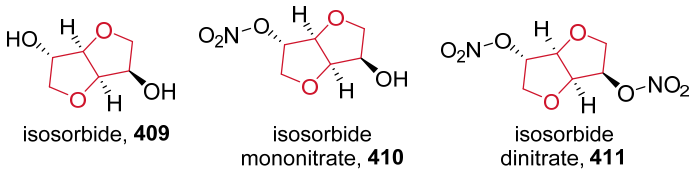
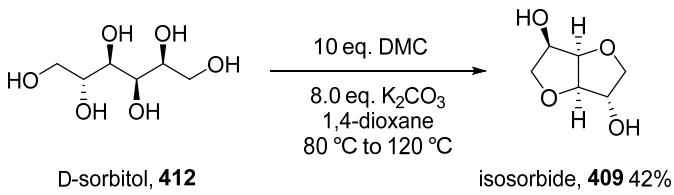


Figure 22. Isosorbide and its derivatives in medicinal chemistry.

4.1.2. The Synthesis of THFs from Sugars

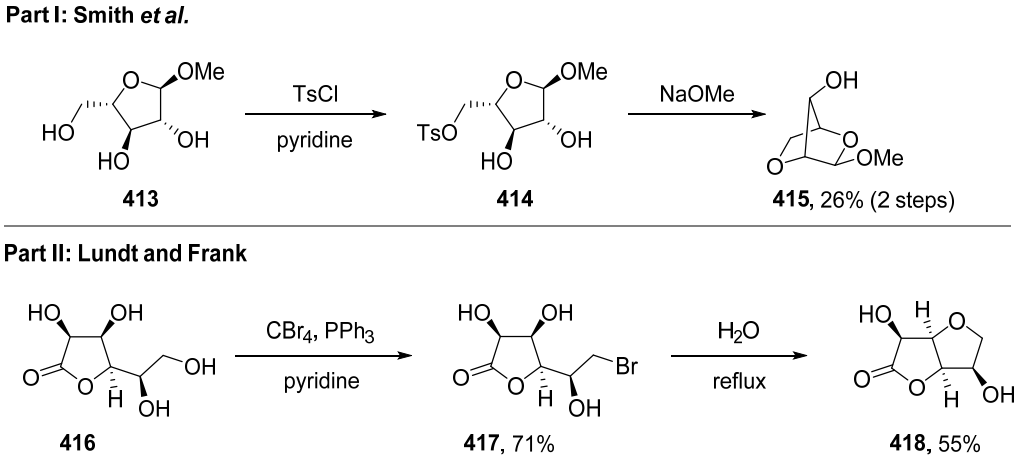
There has been significant interest in the preparation of isosorbide from sorbitol (which in turn is generated from carbohydrate feedstock) under acidic or basic conditions.[222] For example, Rokicki *et al*. reported conditions for the preparation of isosorbide **409** from D-sorbitol **412** using K_2CO_3 as a base and DMC as an activating reagent (**Scheme 97**).[223]



Scheme 97. The preparation of isosorbide form D-sorbitol.

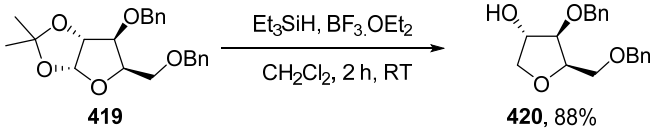
Another method for the cyclization of sugars is to selectively convert a primary alcohol into a leaving group followed by an intramolecular nucleophilic substitution.[224, 225] This

was demonstrated by Smith *et al.*,[226] who reported the cyclization of glycoside **413** in 26% yield through selective reaction of the primary alcohol with TsCl (**Scheme 98**, Part I). Lundt and Frank have reported a similar method for cyclizing lactone **416** in 39% yield over two steps (**Scheme 98**, Part II).[227] A key limitation of this approach is the poor atom economy generally associated with converting a primary alcohol into a leaving group.



Scheme 98. THF synthesis through activation of a primary alcohol as leaving groups.[226, 227]

A more general route to THFs from sugar derivatives is *via* the reduction of a glycoside using Et_3SiH.[228] This transformation can be high yielding, as exemplified by the work of Robins and Ewing (**Scheme 99**).[229] However, this reduction has not been demonstrated on unprotected sugars, which limits its synthetic utility and results in low atom economy.



Scheme 99. Reductive THF synthesis from a protected glycoside.[229]

4.1.3. The Application of *N*,*N*-Dialkylhydrazones in Organic Synthesis

N,*N*-Dialkylhydrazones are a valuable and versatile synthetic tool within organic chemistry (**Figure 23**).[230] One of the main applications of *N*,*N*-dialkylhydrazones **421** is to increase the acidity of carbonyl compounds. Deprotonation at the α-position gives the conjugate base, which can then undergo a reaction with an electrophile.[231] The pK_a of a hydrazone has been calculated to be *ca*. 10 units higher than the parent carbonyl compound and so the conjugate base of a hydrazone can exhibit greater reactivity towards electrophiles. Hydrazones can also undergo addition reactions with nucleophilic alkyl lithium reagents or free radicals to give hydrazine products.[232] Vinyl hydrazones **422** are also useful synthetic building blocks, acting as Michael acceptors with a variety of

nucleophiles. In addition, deprotonation at the γ-position generates a carbanion that can be trapped with electrophiles. Furthermore, vinyl hydrazones **422** are effective dienes for heteronuclear Diels–Alder reactions owing to their electron-rich nature.[233]

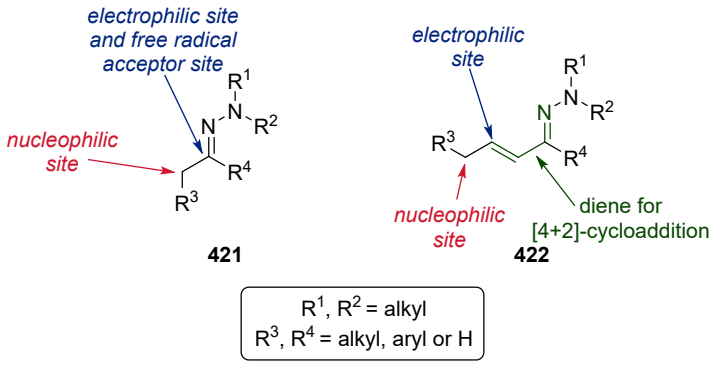
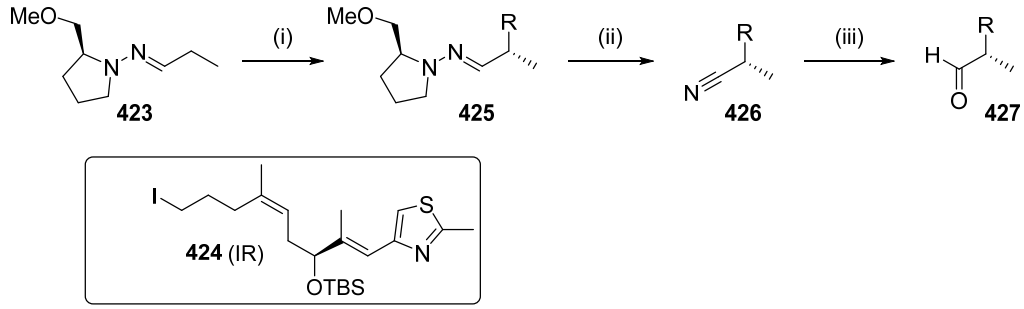


Figure 23. Application of *N,N*-dialkylhydrazones.[230]

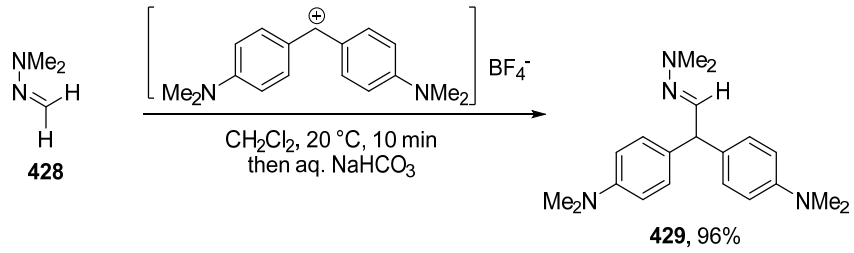
Hydrazone chemistry was developed most notably by Corey and Enders for the stereoselective α-alkylation of ketones using chiral *N,N*-dialkylhydrazones.[234] An application of this approach was reported by Nicolaou *et al.* as part of the total synthesis of Epothilones A and B (**Scheme 100**).[235] Treating (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) hydrazone **423** with lithium diisopropylamide (LDA) and then alkyl iodide **424** gave alkylated product **425** as a single diastereoisomer in 70% yield. Numerous methods have been developed to liberate the original carbonyl functional group from *N,N*-dialkylhydrazones.[236] Nicolaou *et al.* converted hydrazone **425** into aldehyde **427** *via* an oxidative cleavage to give nitrile **426**, which was then reduced using diisobutylaluminium hydride (DIBAL).



Scheme 100. Application of SAMP hydrazone 423 to the synthesis of Epothilones A and B.[235] Reagents and conditions: (i) 1.5 eq. **423**, 1.5 eq. LDA, THF, 0 °C, 8 h; then 1.0 eq. **424**, THF, –100 to –20 °C, 10 h, 70%; (ii) 2.5 eq. MMPP, MeOH:phosphate buffer pH 7 (1:1), 0 °C, 1 h, 80%; (iii) 2.0 eq. DIBAL, PhMe, –78 °C, 1 h, 82%.

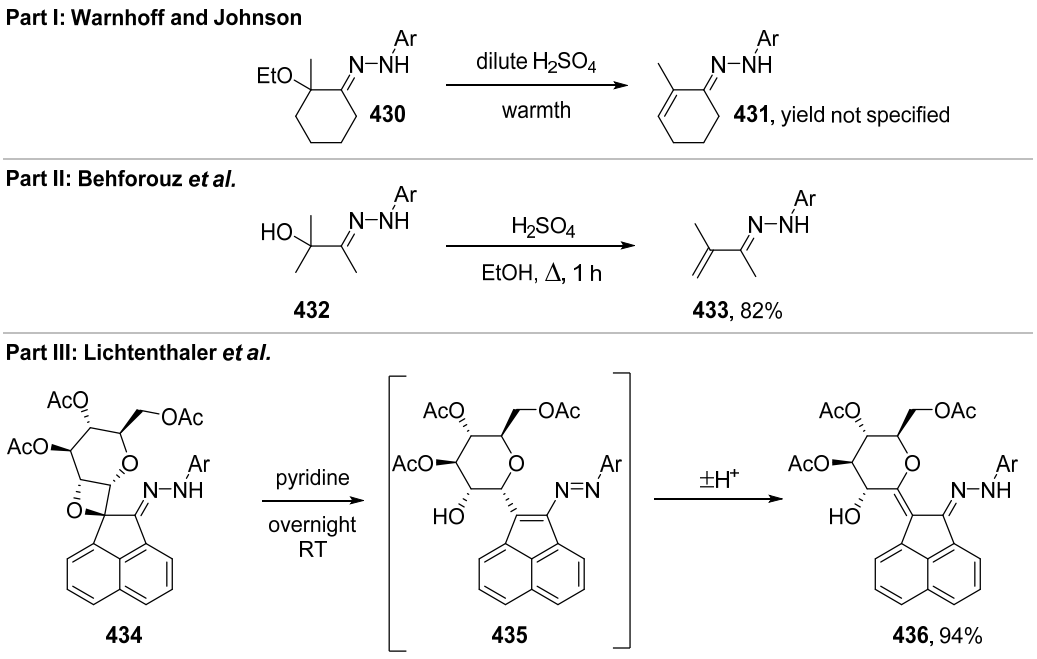
N,N-Dialkylhydrazines have also been used to reverse the inherent reactivity of carbonyl compounds to generate an "acyl anion" equivalent, which can undergo reactions with

different electrophiles.[237] This approach allows ketones to be generated from aldehydes, or for higher aldehydes to be prepared from formaldehyde. For example, Mayr *et al.* explored the alkylation of *N,N*-dialkylhydrazones with benzhydrylium ions, with an example given in **Scheme 101**.[238]



Scheme 101. Alkylation of *N,N*-dialkylhydrazone 428.[238]

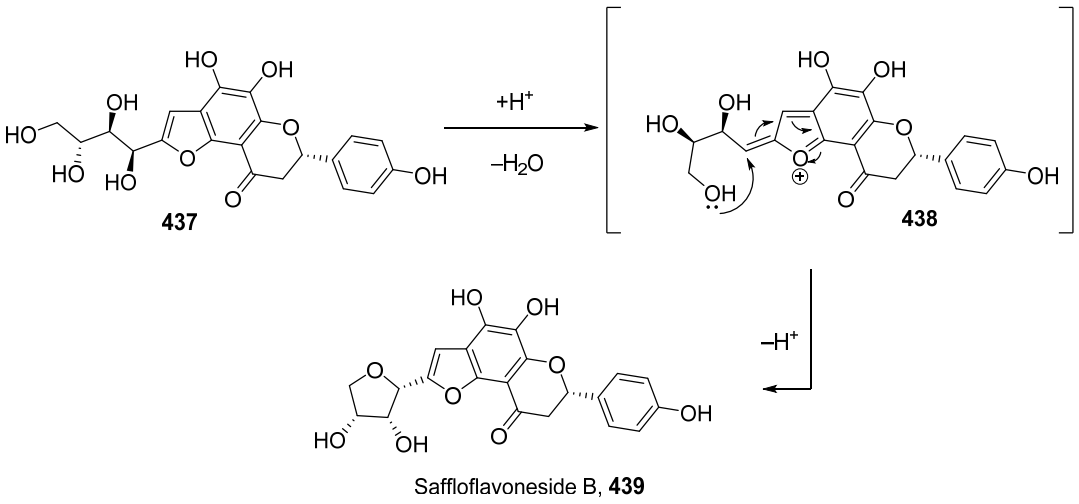
A far less explored synthetic approach is to use a hydrazine to facilitate the elimination of a leaving group adjacent to a carbonyl.[239] In 1953 Warnhoff and Johnson reported that 2,4-dinitrophenylhydrazone **430** underwent an acid mediated elimination of EtOH to give cyclohexene **431** (**Scheme 102**, Part I).[240] Similarly, Behforouz *et al.* reported that hydrazone **432** eliminated water in the presence of H_2SO_4 to give alkene **433** in 82% yield (**Scheme 102**, Part II).[241] In addition, Lichtenthaler *et al.* discovered that treatment of hydrazone **434** with pyridine resulted in ring-opening of the adjacent oxatane to give enol ether **436** in 94% yield (**Scheme 102**, Part III).[242] The authors suggested that the reaction proceeded *via* vinyl diazeneintermediate **435**.



Scheme 102. Elimination of a leaving group adjacent to a hydrazone. Ar = 2,4-dinitrophenyl.

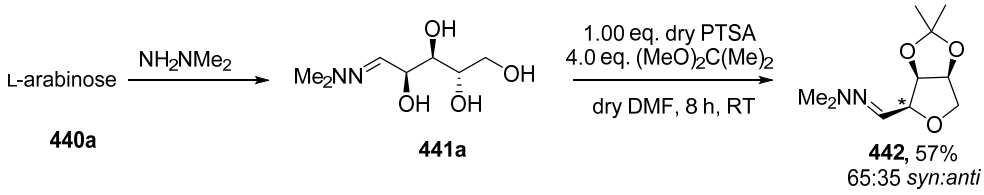
4.1.4. The Cyclization of Reducing Sugars using NH_2NMe_2

Where an electron-rich aromatic group possesses a pendant sugar chain the aromatic ring can induce displacement of the adjacent hydroxyl group to give a resonance-stabilized cationic intermediate, which can be trapped by a pendent hydroxyl group to form a THF. This transformation has been used within synthetic chemistry[243] and can be invoked in a proposed biosynthetic pathway for the formation of Saffloflavonesides B **439** (**Scheme 103**).[244]



Scheme 103. Proposed biosynthetic pathway for the formation of Safflofavoneside B 439.

A similar cyclization of a sugar chain to give a THF was reported by Koóš and Moscher (**Scheme 104**).[245] Hydrazone **441a** was prepared from the condensation reaction of L-arabinose and NH_2NMe_2. Hydrazone **441a** was treated with 1.00 eq. of anhydrous *p*-toluenesulfonic acid (PTSA) and 4.0 eq. of $(MeO)_2CMe_2$ in anhydrous DMF, and THF **442** was isolated in 57% yield as a 65:35 mixture of diastereoisomers.



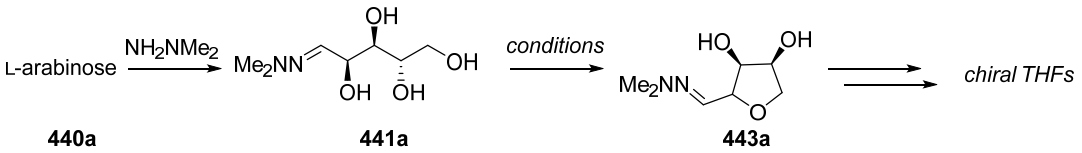
Scheme 104. Koóš and Moscher's cyclization of hydrazone 441a.[245]

4.1.5. Chapter IV Project Outline

The aim of this part of the PhD was to develop a hydrazone-based synthesis of THFs from biomass-derived reducing sugars using sustainable reaction conditions. This would allow for the synthesis of low-molecular weight chiral THFs with control over the absolute

stereochemistry. These products would potentially be valuable building-blocks for chiral sp^3-rich molecular scaffolds.

The reported synthesis of THF **442** by Koóš and Moscher (**Scheme 104**) was a valuable start point for this work.[245] A feature of this reaction is the simultaneous cyclization of the sugar chain and formation of an acetonide from $(MeO)_2CMe_2$. Protecting groups, although often a useful synthetic tool, typically have a detrimental impact on the step economy and atom economy of a synthesis.[246] Therefore an attractive alternative reaction to develop was the cyclization of hydrazone **441a** to give unprotected diol **443a** (**Scheme 105**).



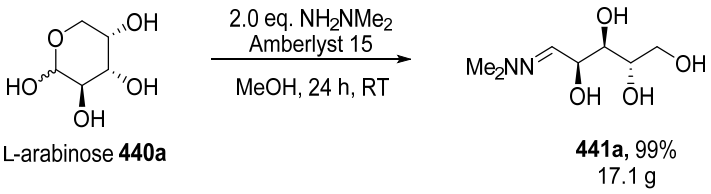
Scheme 105. Chapter IV project aim.

A significant drawback of Koóš and Moscher's reaction conditions that needs to be addressed (**Scheme 104**) was the need for the vigorous exclusion of water, including the use of anhydrous PTSA. Also, DMF has a number of serious environmental drawbacks, so a more sustainable solvent would be advantageous. It would then be important to develop reaction scope with different sugars and to demonstrate the transformation of hydrazone products into a diverse selection of chiral THFs.

4.2. Results and Discussion

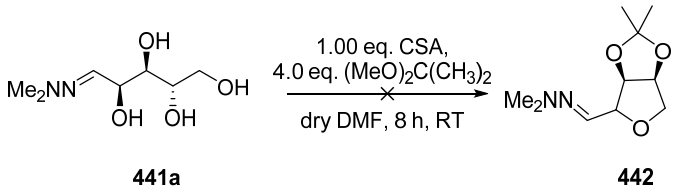
4.2.1. Preliminary Studies

Despite literature precedent, stirring L-arabinose **440a** with NH_2NMe_2 in water at RT failed to afford hydrazone **441a**.[247] Following this, 20 mol% PTSA.H_2O and BF_3.THF were screened as catalysts in MeOH-d_4, $CDCl_3$, D_2O and DMSO-d_6, with PTSA.H_2O/MeOH-d_4 giving the greatest conversion of L-arabinose **440a** after 24 h at RT. This reaction was scaled up using 5.0 mol% PTSA.H_2O in MeOH, which gave the desired hydrazone **441a** in 79% yield. Replacing PTSA.H_2O with Amberlyst 15 acidic resin (0.100 g/mmol) gave hydrazone **441a** in 99% yield on a 90.0 mmol scale, after removal of the resin by filtration (**Scheme 106**).



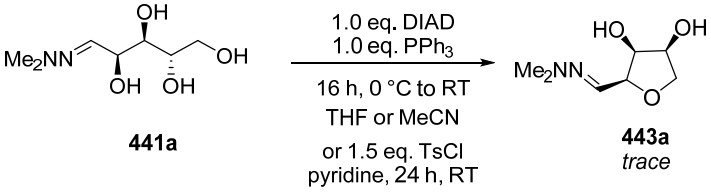
Scheme 106. Synthesis of hydrazone 441a.

As a starting point for the investigation, an attempt was made to reproduce Koóš and Moscher's reported synthesis of THF **442** (**Scheme 104**).[245] Given that anhydrous PTSA is not readily available and difficult to prepare, (±)-camphorsulfonic acid (CSA) was used as an alternative acid (**Scheme 107**). This reaction yielded a complex mixture of products and analysis of the crude ^{1}H NMR spectrum provided no clear evidence for the formation of known THF **442**. Treating hydrazone **441a** with 1.00 eq. of PTSA.H_2O and 4.0 eq. of $(MeO)_2CMe_2$ in MeOH-d_4, $CDCl_3$, D_2O or DMSO-d_6 similarly resulted in the 100% conversion of hydrazone **441a** to give a complex mixture of products.



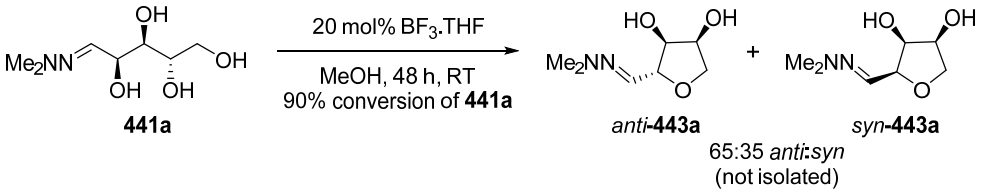
Scheme 107. Failed synthesis of THF 442.

Prior to investigating the acid-catalyzed cyclization of hydrazone **441a**, an attempt was also made at preparing a reference sample of THF **443a** using Mitsonobu conditions. Treating hydrazone **441a** with 1.0 eq. of PPh_3 and 1.0 eq. of diisopropyl azodicarboxylate (DIAD) in either THF or MeCN resulted in the trace formation of cyclized product **443a** (**Scheme 108**).[248] Treating hydrazone **441a** with TsCl in pyridine also resulted in the observation of THF **443a** in a trace quantity.[249] A possible explanation for the failure of this approach is the poor compatibility of the hydrazone functional group with the electrophilic species present under the reaction conditions.



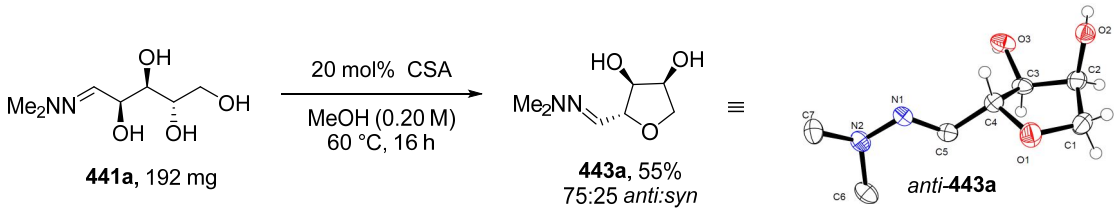
Scheme 108. Attempted synthesis of hydrazone 443a through selective activation of the primary alcohol.

A series of Lewis acids were screened as catalysts for the cyclization of hydrazone **441a** in MeOH at RT. It was observed that using 20 mol% $[Cu(OTf)]_2PhMe$ and $Cu(OTf)_2$ both resulted in decomposition of the substrate after 8 h, while $LiClO_4$, $MgBr_2$ and $Zn(OAc)_2$ resulted in no reaction. However, 20 mol% BF_3.THF catalyzed the formation of THF **443a** as a 65:35 mixture of diastereoisomers, with 90% conversion of **441a** after 48 h at RT (**Scheme 109**).



Scheme 109. Synthesis of THF 443a using BF_3.THF.

The cyclization of hydrazone **441a** in MeOH using 20 mol% BF_3.THF was repeated at 60 °C in order to drive the reaction to completion. The corresponding reaction with 20 mol% CSA was also conducted. Both reactions resulted in 100% conversion of hydrazone **441a** within 16 h, with CSA resulting in fewer impurities (as determined by analysis of the crude ^{1}H NMR spectra). The reaction with CSA was repeated on a 192 mg (1.00 mmol) scale and THF **443a** isolated in 55% yield (**Scheme 110**). By crude ^{1}H NMR spectroscopic analysis the diastereoisomeric ratio was measured as *anti*:*syn* = 75:25. Recrystallization of THF **443a** from CH_2Cl_2 and hexane gave the major diastereoisomer *anti*-**443a** as a single stereoisomer, and the relative stereochemistry was confirmed by single crystal X-ray diffraction.[iii]



Scheme 110. Synthesis of THF 443a using CSA. Ellipsoids are shown at 50% probability level. Only hydrogen atoms belonging to the cyclic core are shown for clarity.

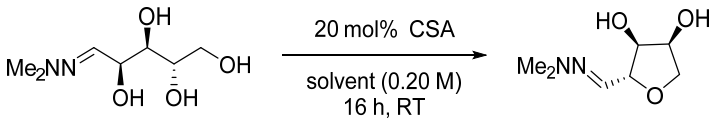
4.2.2. Reaction Optimization

The cyclization of hydrazone **441a** using 20 mol% CSA over 16 h at RT was then investigated using a series of different solvents (**Table 20**). A screen of NMR solvents

[iii] Dr Dejan-Krešimir Bučar and Dr Laure Benhamou are gratefully acknowledged for conducting and analyzing the single crystal X-ray diffraction experiment. Recrystallization was performed by the author.

revealed that no formation of THF **443a** occurred in either D_2O or $CDCl_3$, while using DMSO-d_6 as solvent resulted in *ca*. 10% conversion of hydrazone **441a** (Entries 1–3). The reaction was favored in alcohol solvents (Entries 4–8), with MeOH and ^{n}PrOH giving the highest yields as judged from ^{1}H NMR spectroscopic analysis. DMF, which was used in the cyclization reported by Koóš and Moscher (**Section 4.1.4., Scheme 104**), did facilitate the formation of THF **443a** (Entry 9) but in lower yield than for MeOH and ^{n}PrOH. No significant conversion of hydrazone **441a** was observed where MeCN was used as solvent (Entry 10) and a slow reaction was observed in CPME (Entry 11).

Table 20. Solvent screen for the acid-catalyzed cyclization of hydrazone 443a.



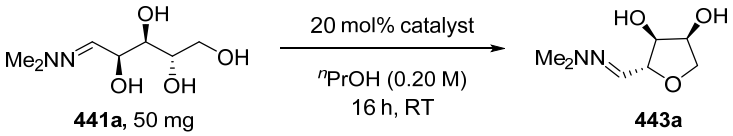
441a, 50 mg — **443a**

Entry	Solvent	Conversion of **441a**/%	Yield **443a**/%[a]	*anti*:*syn* **443a**[a]
1	D_2O	-	0	-
2	$CDCl_3$	-	0	-
3	DMSO-d_6	-	10[b]	-
4	**MeOH**	**50**	**50**	**65:35**
5	EtOH	80	30	65:35
6	**^{n}PrOH**	**100**	**80**	**75:25**
7	^{i}PrOH	40	30	65:35
8	^{n}BuOH	50	35	65:35
9	DMF	65	35	70:30
10	MeCN	20	0	-
11	CPME	25	15	50:50

[a] Determined by analysis of the crude ^{1}H NMR spectrum (using C_6HCl_5 as an internal standard). [b] Estimated without an internal standard.

A series of acids were screened as catalysts for the cyclization, using ^{n}PrOH as reaction solvent (**Table 21**). All the strong acids were effective at catalysing the cyclization (Entries 1–5) while AcOH resulted in no reaction (Entry 6). Both TFA and CSA were effective catalysts for the cyclization, with 80% yields of THF **443a** calculated using ^{1}H NMR spectroscopy. CSA and TFA are of similar cost (*ca*. £200/kg of TFA compared to *ca.* £150/kg CSA)[250] but the molecular weight of CSA is approximately twice that of TFA. On these grounds TFA was chosen as the more economical catalyst for further work.

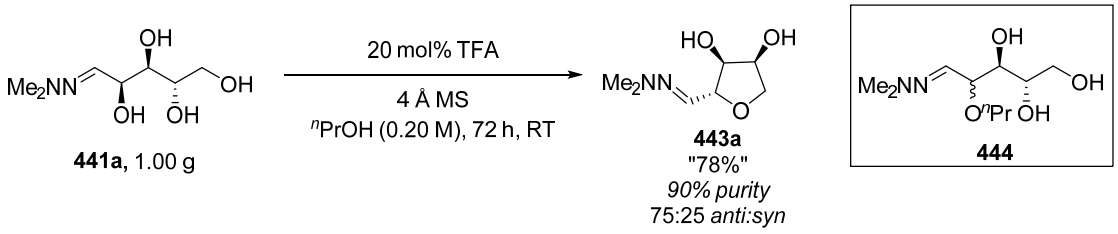
Table 21. Cyclization catalyst screen.



Entry	Catalyst	Conversion **441a**/%	Yield **443a**/%[a]	*anti*:*syn* **443a**[a]
1	**CSA**	**100**	**80**	**75:25**
2	HCl (4 M in dioxane)	70	50	75:25
3	conc. H_2SO_4[b]	40	25	60:40
4	PTSA.H_2O	50	35	65:35
5	**TFA**	**80**	**80**	**75:25**
6	AcOH	0	0	-

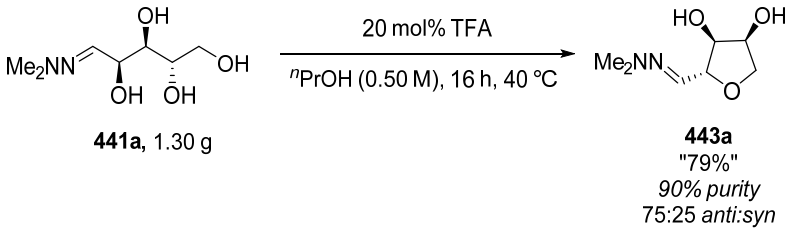
[a] Determined by analysis of the crude ^{1}H NMR spectrum (using C_6HCl_5 as an internal standard). [b] 10 mol%.

The reactions in **Table 20** and **Table 21** suggested that ^{n}PrOH was marginally the best solvent for the cyclization and TFA was the best catalyst. However, when these conditions were used on a 1.00 g scale two serious problems were observed. Firstly the reaction consistently took 72 h to reach completion, even when 4 Å molecular sieves were added as a dehydrating agent (**Scheme 111**). Secondly, the THF **443a** could not be separated from an impurity by flash column chromatography, giving THF **443a** in only 90% purity. While the impurity was not isolated or characterized, the ^{1}H NMR spectrum was consistent with solvolysis product **444**.



Scheme 111. Cyclization of hydrazone 441a in ^{n}PrOH at RT.

Heating the reaction to 40 °C and increasing the reaction concentration to 0.50 M had a significant impact on the reaction time, with 100% conversion of hydrazone **441a** observed after 16 h (**Scheme 112**). This reaction was conducted without 4 Å molecular sieves, with no detrimental impact on the yield of THF **443a**. However, impurity **444** was still present following column chromatography and so these conditions required further optimization.

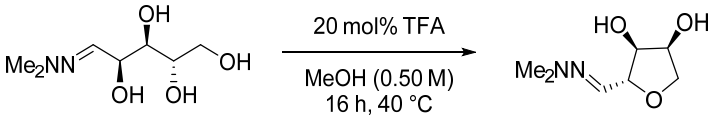


441a, 1.30 g

443a
"79%"
90% purity
75:25 *anti:syn*

Scheme 112. Cyclization of hydrazone 441a in ^{n}PrOH at 40 °C.

When the reaction solvent was switched to MeOH, THF **443a** was isolated in 67% yield as a 75:25 mixture of diastereoisomers in excellent purity following flash column chromatography (**Scheme 113**). These reaction conditions were taken as the optimized reaction conditions for further investigation.



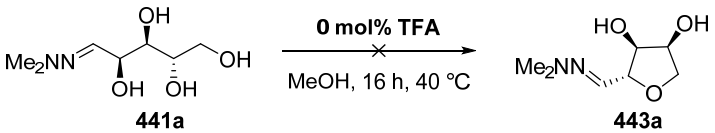
441a, 1.26 g

443a, 67%
75:25 *anti*:*syn*

Scheme 113. Optimized cyclization of hydrazone 441a.

4.2.3. Mechanistic Investigations

As a control reaction, the optimized reaction conditions described in **Scheme 113** were replicated without the TFA additive being present (**Scheme 114**). Analysis of the crude ^{1}H NMR spectrum showed that this resulted in no formation of THF **443a** and no evidence for the conversion of hydrazone **441a** was observed. This control reaction confirmed that TFA was acting as a catalyst for the formation of THF **443a**.

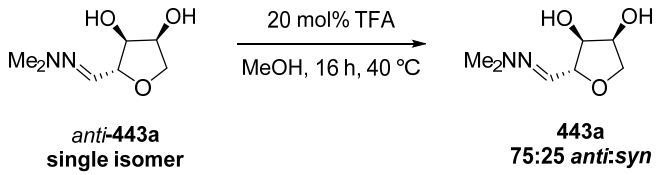


441a

443a

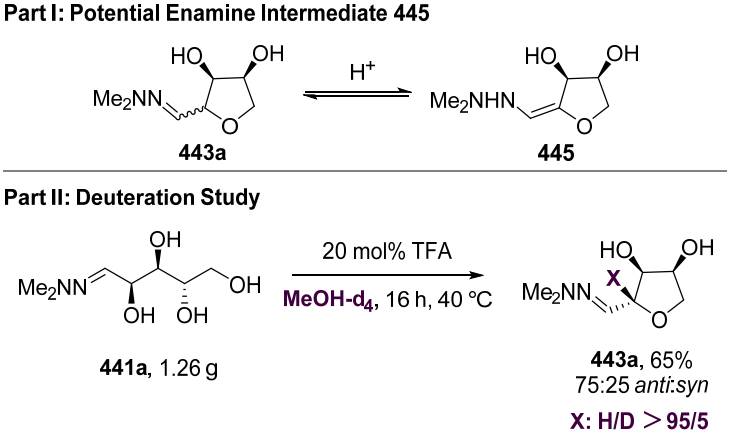
Scheme 114. Control reaction with no TFA additive.

Recrystallization of THF **443a** from hot CPME gave the major diastereoisomer *anti*-**443a** in high purity. The optimized cyclization conditions in **Scheme 113** were replicated, but hydrazone **441a** was substituted for an isomerically pure sample of THF *anti*-**443a** (**Scheme 115**). Analysis of the crude ^{1}H NMR spectrum indicated that THF **443a** had epimerized under the reaction conditions to give a 75:25 mixture of *anti*- and *syn*-diastereoisomers. This implied that the diastereoselectivity of the cyclization reaction was under thermodynamic control.



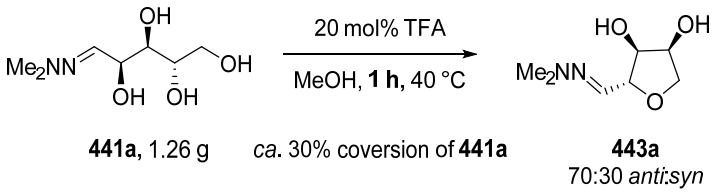
Scheme 115. Epimerization of *anti*-443a under the optimized cyclization conditions.

The epimerization of THF **443a** could be explained by a reversible cyclization reaction, or alternatively *via* the formation of enamine intermediate **445** (**Scheme 116**, Part I). In order to gain insight, the optimized cyclization reaction of hydrazone **441a** (**Scheme 113**) was replicated using MeOH-d_4 as solvent. This resulted in the formation of THF **443a** as a 75:25 mixture of *anti*- and *syn*-diastereoisomers, which was isolated in 65% yield (**Scheme 116**, Part II). No measurable incorporation of deuterium was observed at the position adjacent to the hydrazone, which suggests that epimerization is not occurring *via* enamine **445**.



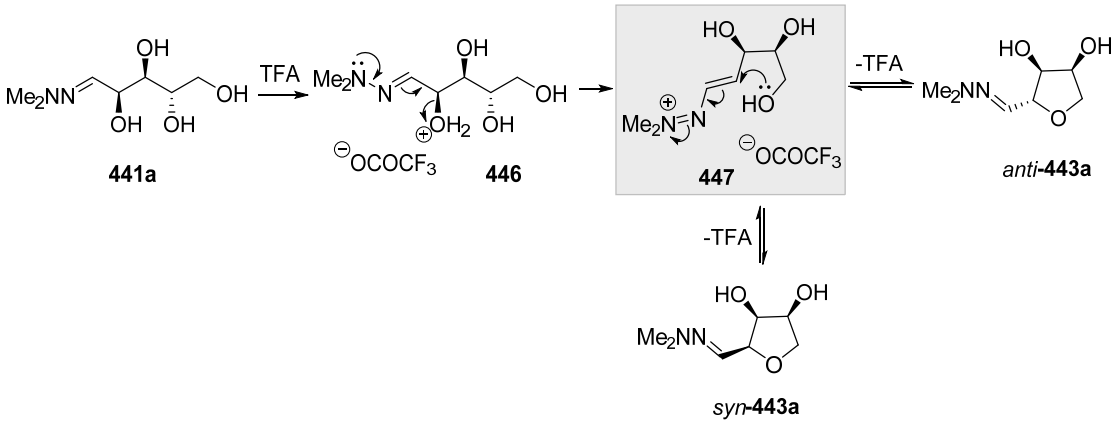
Scheme 116. Potential enamine intermediate 445 and Cyclization of hydrazone 441a in MeOH-d_4.

As a final mechanistic experiment, the optimized cyclization reaction was replicated, but the reaction quenched after only 1 h. Analysis of the crude ^{1}H NMR spectrum implied *ca.* 30% conversion of hydrazone **441a** and formation of THF **443a** as a 70:30 mixture of *anti*- and *syn*-diastereoisomers (**Scheme 117**). This compares to a 75:25 *d.r.* when the same reaction was conducted over 16 h (**Scheme 113**). While the difference in *d.r.* at 1 h and 16 h was only small, the observation was consistent with a reaction where THF **443a** was initially formed with a *d.r.* < 75:25, but equilibration over 16 h increased the proportion of the *anti*-diastereoisomer present.



Scheme 117. Cyclization of hydrazone 441a after 1 h.

A suggested mechanistic pathway is given in **Scheme 118**. The protonation of compound **441a** to give intermediate **446** and subsequent elimination of water would result in the formation of a vinyldiazenium species **447**. Cyclization of vinyldiazenium intermediate **447** could yield either *anti*- or *syn*-**443a**, depending on the conformation of the intermediate. The experiments detailed in **Scheme 115** and **Scheme 117** implied that this cyclization was reversible, ultimately giving the thermodynamic mixture of *anti*- and *syn*-diastereoisomers.

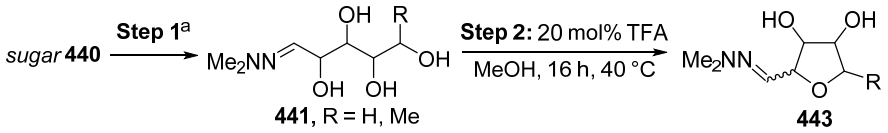


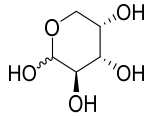
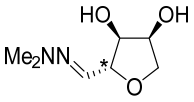
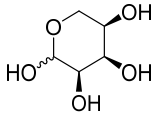
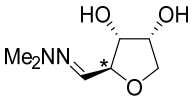
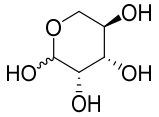
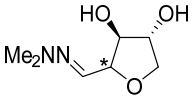
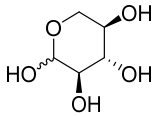
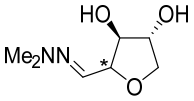
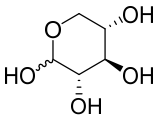
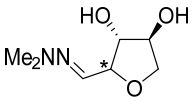
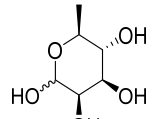
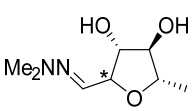
Scheme 118. Proposed mechanistic pathway for the formation of THF 443a.

4.2.4. Cyclization Scope

The optimized synthetic sequence was applied to a series of reducing sugars, with the results detailed in **Table 22**. As discussed previously, L-arabinose was efficiently converted to hydrazone **441a** and this was converted to THF **443a** in 67% yield as a 75:25 mixture of *anti*- and *syn*-diastereoisomers on a 1.26 g (6.60 mmol) scale (Entry 1). In addition, the cyclization step was scaled up to use 20.0 g (104 mmol) of hydrazone **441a** with no notable drop in yield or stereoselectivity.

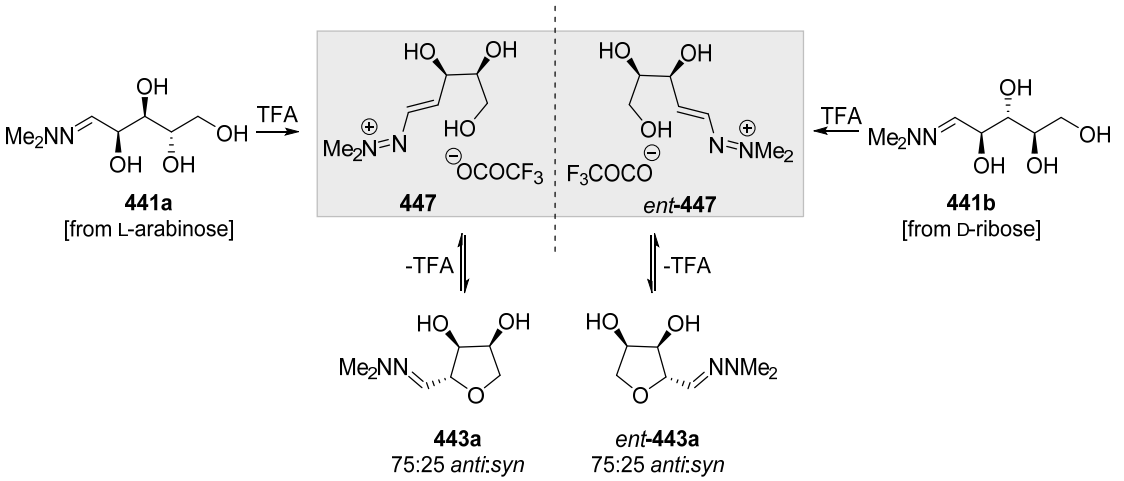
Table 22. Hydrazone-mediated cyclization of sugars 440.



Entry	Sugar **440**	**Step 1** yield/%	THF **443**[b]	**Step 2** yield%	*d.r.*[c]
1	 L-arabinose **440a**	99	 **443a**	67 (66)[d]	75:25
2	 D-ribose **440b**	98	 *ent*-**443a**	59	75:25
3	 D-lyxose **440c**	98	 **443b**	66	55:45
4	 D-xylose **440d**	not isolated	 **443b**	61[e]	55:45
5	 L-xylose *ent*-**440d**	not isolated	 *ent*-**443b**	57[e]	55:45
6	 L-rhamnose **440e**	99	 **443c**	69	60:40

[a] **Step I** reagents and conditions: 2.0 eq. NH_2NMe_2, Amberlyst 15, MeOH, 24 h, RT. [b] **Step II** conducted on a 6.00–6.70 mmol scale unless otherwise stated. [c] Determined by analysis of the crude ^{1}H NMR spectrum. [d] Reaction conducted using 20.0 g (104 mmol) of hydrazone **441a**. [e] Yield over two steps from xylose.

D-Ribose **440b** was converted into the corresponding hydrazone **441b** in 98% yield and without need for purification (**Table 22**, Entry 2). Under the optimized cyclization conditions hydrazone **441b** was converted into THF *ent*-**443a** in 59% yield as a 75:25 mixture of *anti*- and *syn*-diastereoisomers. According to the mechanism proposed in **Scheme 118**, the cyclization of arabinose- and ribose-derived hydrazones **441a** and **441b** proceed *via* enantiomeric vinyldiazenium intermediates (**Scheme 119**). The observation that both reactions resulted in the same ratio of *anti*- and *syn*-diastereoisomers is therefore consistent with the proposed mechanism.



Scheme 119. Cyclization of hydrazone 441a and 441b through enantiomeric vinyldiazenium intermediates.

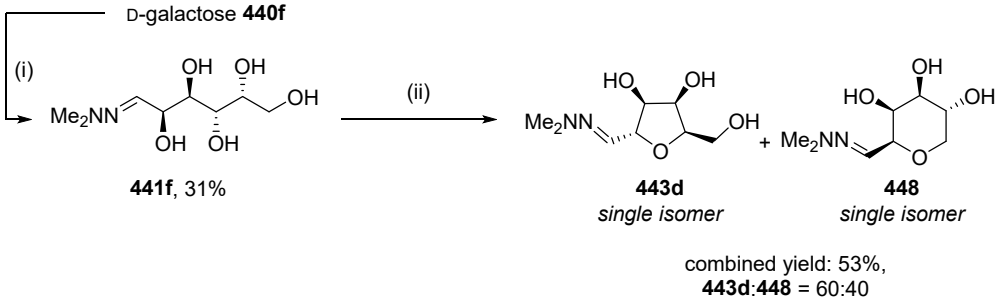
The methodology was also extended to D-lyxose **440c**, with the corresponding hydrazone prepared in 98% isolated yield (**Table 22**, Entry 3). The optimized cyclization step gave THF **443b** in 66% isolated yield as a 55:45 mixture of diastereoisomers. Given the poor diastereoselectivity of this reaction, the relative stereochemistry of the major diastereoisomer was not examined.

The reaction of D-xylose **440d** with NH_2NMe_2 under the optimized conditions resulted in 100% conversion of **440d** within 24 h and analysis of the ^{1}H NMR spectrum in DMSO-d_6 confirmed the formation of the corresponding hydrazone. However, the target hydrazone was not the only species observed by ^{1}H NMR spectroscopy so it was not possible to calculate an isolated yield. Subjecting the crude hydrazone to the cyclization conditions gave THF **443b** in 61% isolated yield over two steps (**Table 22**, Entry 4). Using the same approach, L-xylose *ent*-**440c** was converted into *ent*-**443b** with a comparable yield and diastereoselectivity (Entry 5).

The optimized synthetic pathway was also applied to deoxy sugar L-rhamnose **440e** (**Table 22**, Entry 6). The corresponding hydrazone was accessed in 99% yield and this was cyclized to give THF **443c** as a 60:40 mixture of diastereoisomers in 69% isolated yield without modification of the cyclization conditions.

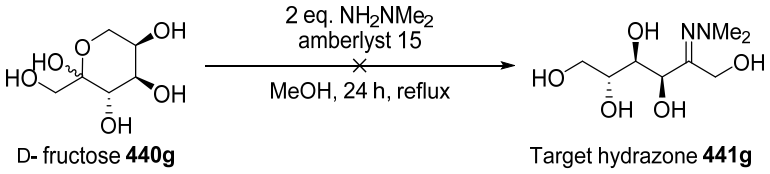
The optimized conditions for hydrazone synthesis were also applied to D-galactose (**Scheme 120**). This reaction was slower than had been observed with the pentoses, but significant conversion of the starting material had occurred after 3 days at RT. It was necessary to purify the reaction by flash column chromatography, with hydrazone **441f**

isolated in 31% yield. The optimized cyclization conditions gave a 60:40 mixture of THF **443d** and tetrahydropyran **448** in 53% yield. Both compounds were formed as single stereoisomers and were separated by flash column chromatography.



Scheme 120. Cyclization of galactose-derived hydrazone 441f. Reagents and conditions: (i) 2.0 eq. NH_2NMe_2, Amberlyst 15, MeOH, 72 h, RT; (ii) 20 mol% TFA, MeOH, 16 h, 40 °C.

An attempt was made to extend the methodology to D-fructose **440g**. Under the optimized condensation conditions very little conversion of D-fructose **440g** was observed. Heating the reaction at reflux for 24 h improved the conversion of D-fructose **440g** but yielded a complex mixture of products (**Scheme 121**).

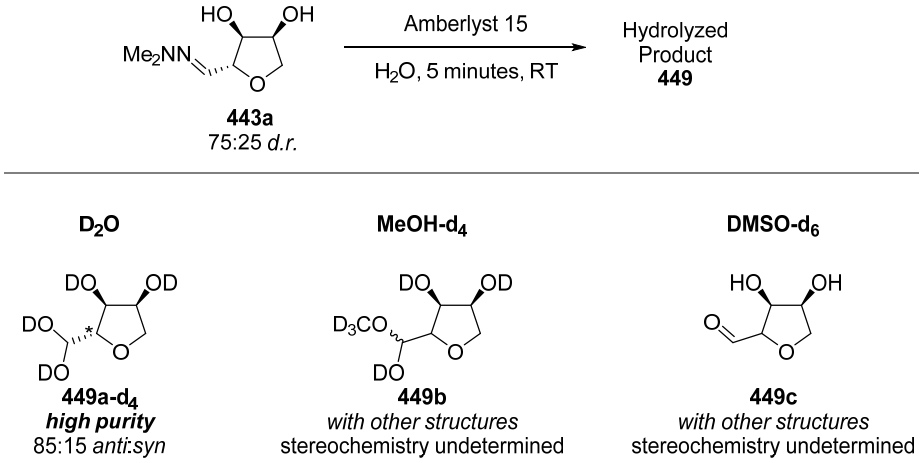


Scheme 121. Unsuccessful reaction of D-fructose with NH_2NMe_2.

4.2.5. Functional Group Manipulation of Cyclized Products

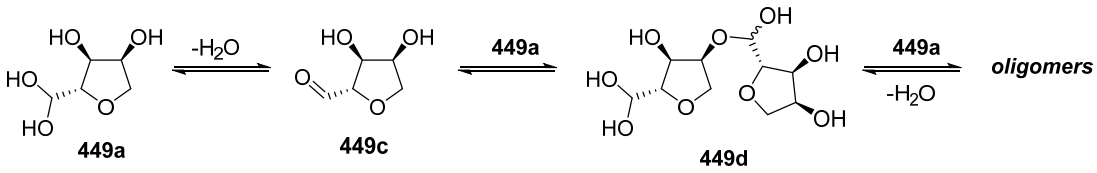
Treatment of hydrazone **443a** with an excess quantity of Amberlyst 15 acidic resin (1.00 g/mmol **443a**) in water at RT resulted in rapid hydrolysis of the hydrazone. The resin was removed by filtration and the filtrate was then concentrated and lyophilized to yield a white gum. ^{1}H and ^{13}C NMR data of the compound in D_2O suggested that the hydrolyzed product **449** existed as a hydrate **449a-d$_4$**, as depicted in **Scheme 124**. The NMR data was consistent with an 85:15 mixture of diastereoisomers, without any impurities [^{13}C NMR (150 MHz; D_2O) 90.4 (*C*$(OD)_2$ *anti*-**449a-d$_4$**), 89.2 (*C*$(OD)_2$ *syn*-**449a-d$_4$)**; full characterization in Chapter VI]. However, analysis of the ^{1}H and ^{13}C NMR spectra in MeOH-d_4 revealed a more complex mixture of compounds, with the majority of material existing as a compound consistent with hemiacetal **449b** [^{13}C NMR (150 MHz; MeOH-d_4) 98.9 (*C*$(OD)(OCD_3)$), 98.7 (*C*$(OD)(OCD_3)$)]. Analysis of ^{1}H and ^{13}C NMR spectra in DMSO-d_6 revealed an even more complex mixture of products, but

with evidence for aldehyde **449c** [^{1}H NMR (600 MHz; DMSO-d_6) 9.56 (1H, d, J = 2.3, C(O)*H*); ^{13}C NMR (150 MHz; DMSO-d_6) 201.9 (*C*(O)H)].



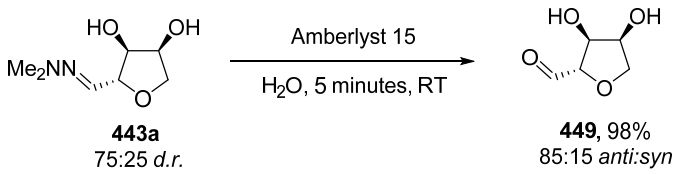
Scheme 122. Hydrolysis of 443a and the identity of hydrolyzed product 449 in NMR solvents.

A possible explanation for this observation is that compound **449** undergoes a reversible condensation when concentrated to form an oligomeric structure (**Scheme 123**). Given that hydrolyzed product **449** was formed in water, it is reasonable to assume it was formed as hydrate **449a**. If upon condensation hydrate **449a** eliminated a molecule of water to give aldehyde **449c**, then this could react with a second molecule of **449a** to give a dimer, such as compound **449d**. This could then undergo further dehydration reactions to give a complex mixture of oligomers. An IR spectra of the neat gum only possessed one weak peak at 1720 cm^{-1} in the region 1650–1750 cm^{-1}, suggesting that the solid state structure is not a monomeric aldehyde.



Scheme 123. Proposed reversible oligomerization of hydrolyzed product 449.

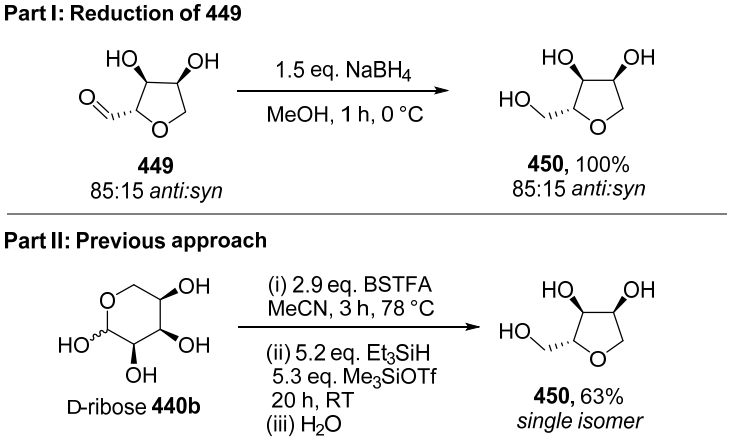
Without a definite structure of hydrolyzed product **449**, it is not possible to definitively assign a yield for the hydrolysis reaction (**Scheme 121**). However, if it is assumed that during lyophilization one molecule of water is eliminated for every molecule of hydrate **449'**, then the isolated yield for compound **449** was 98%. For the remainder of Chapter IV, compound **449** is depicted as a free aldehyde (as in **Scheme 124**), however it is recognized that this is a simplification of its solid-state structure.



Scheme 124. Hydrolysis of hydrazone 443a.

It is also notable that the reaction proceeds with an increase in the diastereoisomeric ratio. Under the same reaction conditions isomerically pure *anti*-**443a** epimerized to give the same 85:15 mixture of diastereoisomers. It is therefore likely that the diastereoselectivity observed is due to thermodynamic control.

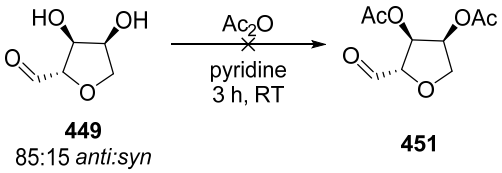
Compound **449** was reduced using $NaBH_4$ in MeOH to form triol **450**, but isolation of the product was initially problematic. Flash column chromatography (using either silica or $MgSiO_3$) failed to yield pure product, in part because of the high polarity of triol **450**. Amberlyst IRA743 boron scavenger was also trialled but this too failed to yield pure product. However, quenching the reaction with AcOH and subsequent treatment with a mixture of Amberlyst 15 acidic resin and Amberlyst A26 basic resin gave triol **450** in quantitative yield as an 85:15 mixture of diastereoisomers (**Scheme 125**, Part I). The major product has previously been prepared through the universal protection of D-ribose using bis(trimethylsilyl)trifluoroacetamide (BSTFA), reduction with TMSOTf/Et_3SiH and subsequent deprotection (**Scheme 125**, Part II). This allowed the relative stereochemistry of triol **450** (and, by implication, that of compound **449**) to be confidently determined based on comparison with literature data.[251]



Scheme 125. Reduction of compound 449 and previous approach to triol 450.[256]

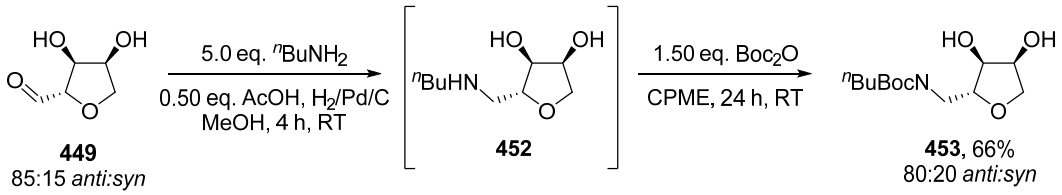
Compound **449** was treated with a 1:1 mixture of Ac_2O in pyridine with the aim of universal acylation to give aldehyde **451** (**Scheme 126**). However, analysis of the crude

^{1}H NMR spectrum indicated 100% conversion of compound **449** to give a complex mixture of products, with no clear evidence for the target aldehyde **451**.



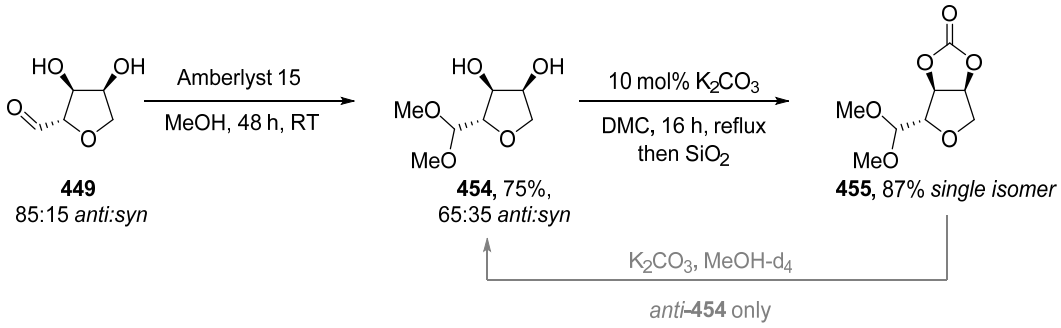
Scheme 126. Failed acylation of compound 449.

Compound **449** was also treated with 5.0 eq. of ^{n}BuNH$_2$, 50 mol% AcOH and 10% Pd/C in MeOH in order to generate amine **452** (**Scheme 127**). This resulted in 100% conversion of compound **449** after 4 h, upon which the reaction mixture was filtered through Celite and concentrated. The crude amine **452** was too polar to purify directly by flash column chromatography, so it was dissolved in CPME and treated with Boc$_2$O. This generated carbamate **453** in 66% isolated yield as an 80:20 mixture of diastereoisomers.



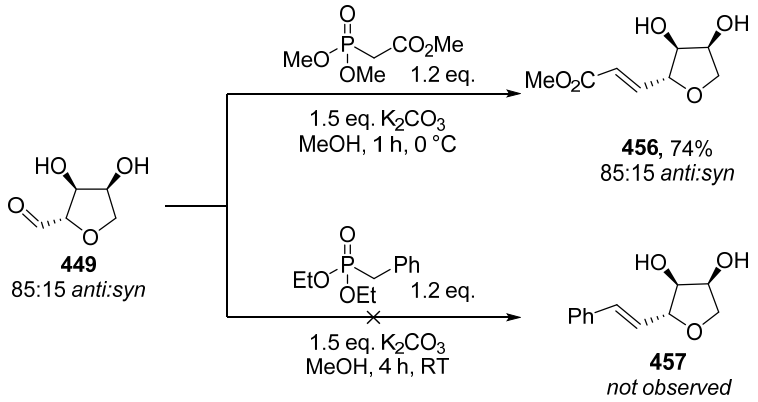
Scheme 127. Reductive amination of compound 449.

Treatment of compound **449** with Amberlyst 15 in MeOH resulted in the formation of dimethyl acetal **454** in 75% yield as a 65:35 mixture of diastereoisomers (**Scheme 128**). In order to assign the stereochemistry, acetal **454** was treated with 10 mol% K_2CO_3 in dimethyl carbonate (DMC) and the reaction heated at reflux for 16 h. This gave the corresponding carbonate **455** as a single *anti*-isomer in 87% yield following purification using a silica plug. The relative stereochemistry of carbonate **455** was determined from its ^{1}H NMR spectrum by analysis of proton coupling constants, owing to the more rigid nature of the THF. Treatment of carbonate **455** with K_2CO_3 in MeOH-d$_4$ gave diol *anti*-**454** as a single isomer, confirming the stereochemistry of the acetal formed. Repeating the carbonate formation step without the silica plug purification, followed by carbonate hydrolysis with K_2CO_3 in MeOH gave acetal **455** as a 65:35 mixture of diastereoisomers. This suggested that *syn*-**455** may readily isomerize on silica to give the thermodynamically more stable *anti*-**455**.



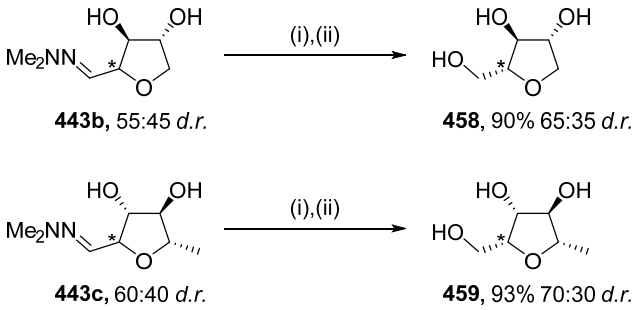
Scheme 128. Dimethyl acetal formation.

Treatment of compound **449** with trimethylphosphonoacetate and K_2CO_3 in MeOH resulted in the formation of olefin **456** in 74% isolated yield (**Scheme 129**). The alkene was formed with excellent *E*-selectivity and the 85:15 mixture of diastereomers reflects that of compound **449**. However, no reaction was observed when compound **449** was treated with diethyl benzylphosphonate under similar conditions, potentially due to the higher pK_a or the phosphonate.



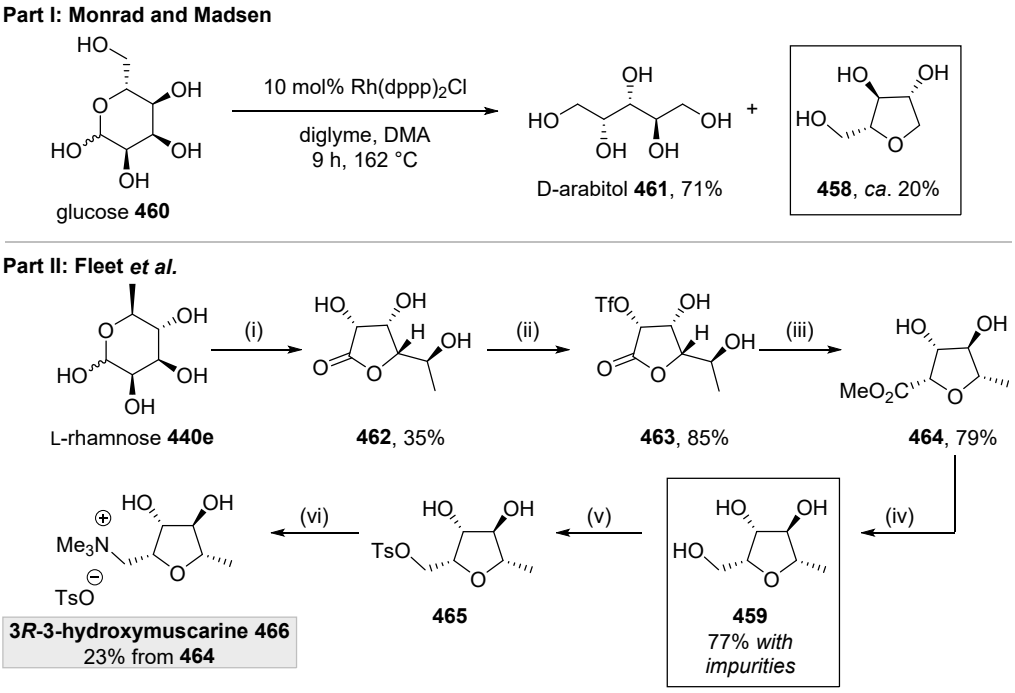
Scheme 129. Olefination of compound 449.

The hydrolysis/reduction sequence was also applied to the hydrazones **443b** and **443c**, derived from D-xylose and L-rhamnose respectively (**Scheme 130**). In both cases the hydrazones were transformed to the corresponding triols in good yield and with an increased diastereoisomeric ratio.



Scheme 130. Hydrolysis and reduction of hydrazones 458 and 459. Reagents and conditions: (i) Amberlyst 15, H_2O, 5 minutes, RT; (ii) $NaBH_4$, MeOH, 1 h, 0 °C.

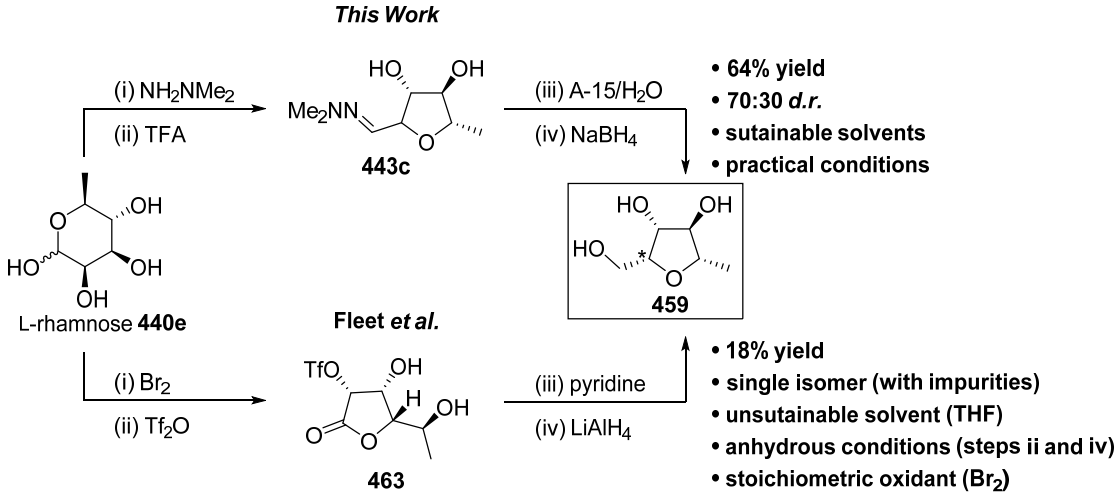
It was possible to confirm the relative stereochemistry of triol **458** as the major isomer has previously been reported by Monrad and Madsen as a by-product from a rhodium-catalyzed decarbonylation of D-glucose (**Scheme 131**, Part I). [252] The major isomer of triol **459** was prepared by Fleet *et al.* as part of the total synthesis of muscarine analogue 3*R*-3-hydroxymuscarine from L-rhamnose (**Scheme 131**, Part II), so again the relative stereochemistry was established.[253]



Scheme 131. Madsen's decarbonylation of D-glucose and Fleet's total synthesis of 3*R*-3-hydroxymuscarine from L-rhamnose. Reagents and conditions: (i) Br_2; (ii)Tf_2O; (iii) pyridine, MeOH; (iv) $LiAlH_4$; (v) TsCl; (vi) NMe_3.

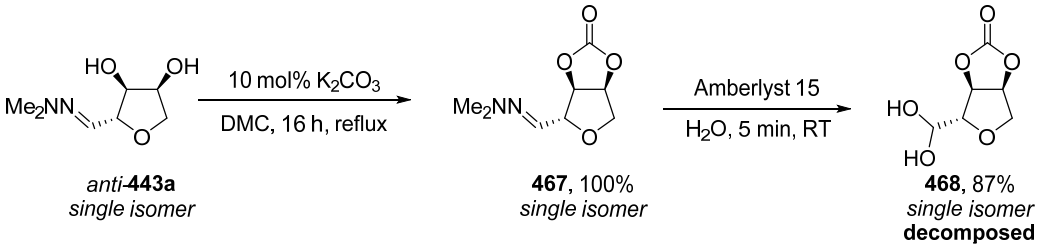
It is interesting to compare Fleet's synthesis of triol **459** (**Scheme 131**) with the synthesis described in **Scheme 130**. Both approaches synthesise triol **459** over 4 steps without the use of protecting groups (**Scheme 132**). Fleet's approach gives triol **459** as a single stereoisomer but in a lower overall yield. Perhaps the most significant advantages of the

new methodology for the synthesis of triol **459** is the improvement in atom economy and redox economy. The new methodology also avoids using water-sensitive Tf_2O and $LiAlH_4$, so it is potentially more amenable to large-scale synthesis.



Scheme 132. Comparison of different approaches to triol 459.[253]

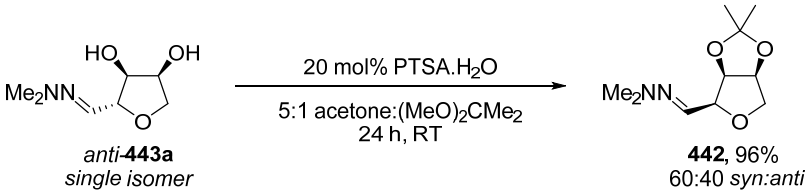
As was mentioned previously, THF *anti*-**443a** was isolated as a single stereoisomer through recrystallization from hot CPME. The transformation of this product into (single isomer) THFs was investigated. The cyclization of diol *anti*-**443a** using 10 mol% K_2CO_3 in DMC gave carbonate **467** as a single isomer in quantitative yield (**Scheme 133**). Hydrolysis of the hydrazone with Amberlyst 15 in water gave a product which, in D_2O, was consistent with hydrate **468** by ^1H NMR spectroscopic analysis, in 87% yield as a single stereoisomer. However, this product was unstable over a period of approximately 24 h in D_2O and was not fully characterized.



Scheme 133. Cyclization of diol *anti*-443a with DMC.

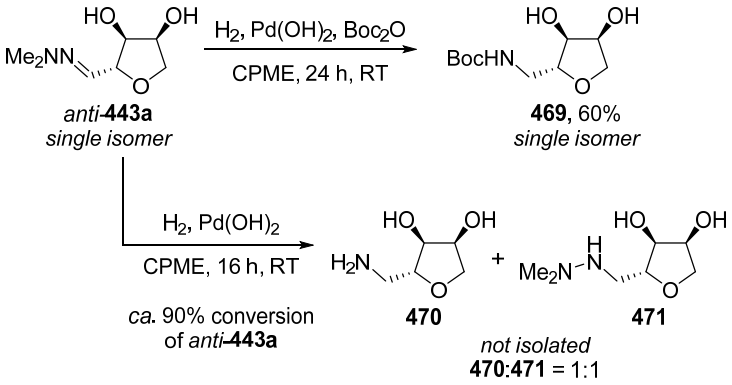
Diol *anti*-**443a** was converted into acetonide **442** in good yield using acetone, $(MeO)_2CMe_2$ and 20 mol% PTSA.H_2O (**Scheme 134**). This reaction occurred with partial inversion of the epimerizable stereocentre, with acetonide **442** isolated as a 60:40 mixture of *syn*- and *anti*-diastereoisomers. The epimerization potentially occurred through acid-mediated reversible ring-opening of the THF under the reaction conditions. The 60:40

diastereoisomeric ratio of acetonide **442** is comparable with 65:35 ratio reported by Koóš and Moscher for the cyclization of arabinose hydrazone **441a** in the presence of $(MeO)_2CMe_2$ in DMF (**Section 4.1.4., Scheme 104**).[245]



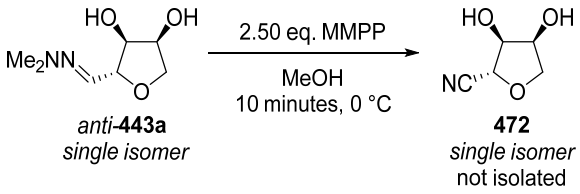
Scheme 134. Synthesis of acetonide 442.

Reduction of hydrazone *anti*-**443a** using hydrogen gas in the presence of $Pd(OH)_2$ in CPME in the presence of Boc_2O gave carbamate **469** in 60% yield as a single stereoisomer (**Scheme 135**).[254] Conducting the reaction in the absence of Boc_2O resulted in the formation of two compounds consistent with amine **470** and hydrazine **471**, with *ca.* 90% conversion of hydrazone *anti*-**443a**.



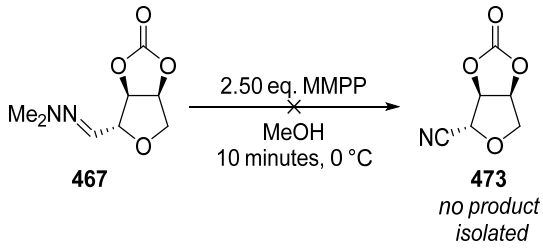
Scheme 135. Reduction of hydrazone *anti*-443a.

It is established that *N*,*N*-dialkylhydrazones can be converted to the corresponding nitrile through oxidation with magnesium monoperoxyphthalate (MMPP).[255] Treating hydrazone *anti*-**443a** with 2.50 eq. of MMPP in MeOH at 0 °C resulted in 100% conversion of hydrazone *anti*-**443a** within 10 minutes (**Scheme 136**). Analysis of the crude product revealed a product consistent with nitrile **472** as a single isomer with only minor impurities. However, after a number of attempts it was not possible to isolate a purified sample of the compound. Why nitrile **472** was so difficult to isolate is unclear, but it could be due to poor stability on silica, volatility or simply a poor reaction yield. The reaction was also attempted using 1.20 eq. of MMPP, but this reaction failed to reach completion after 24 h.



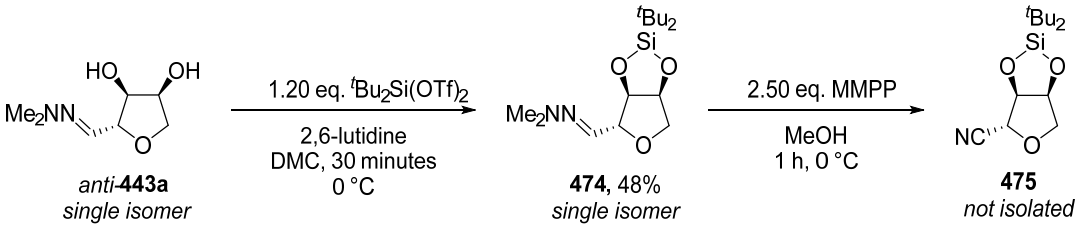
Scheme 136. Attempted oxidation of diol *anti*-443a.

The oxidation conditions were also applied to carbonate **467** (**Scheme 137**). This resulted in rapid conversion of the starting material but no product was isolated from this reaction. This result could be due to the instability of the cyclic carbonate group under the reaction conditions.



Scheme 137. Attempted oxidation of carbonate 467.

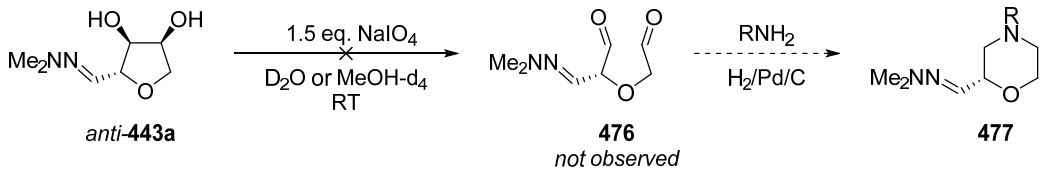
In an attempt to find a suitable substrate for the oxidative hydrazone cleavage, diol *anti*-**443a** was converted into cyclic silyl ether **474**. Treating diol *anti*-**443a** with $^{t}Bu_2Si(OTf)_2$ in pyridine at 0 °C resulted in the formation of silyl ether **474** but with significant epimerization. However, the epimerization was avoided by using DMC as a solvent and 2,6-lutidine as a base, giving the desired silyl ether **474** in 48% yield as a single isomer (**Scheme 138**). Oxidation with MMPP gave a product consistent with nitrile **475** as a single diastereoisomer, but column chromatography failed to recover the target material.



Scheme 138. Synthesis and oxidation of cyclic silyl ether 474.

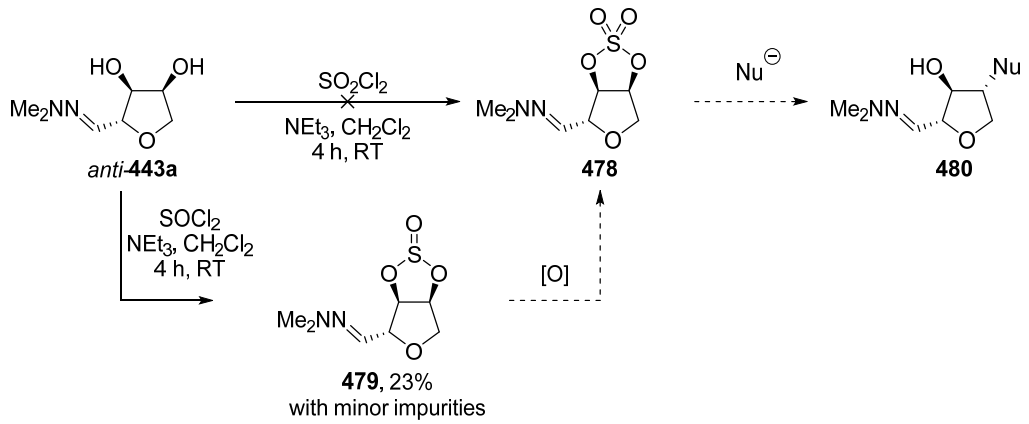
A potentially useful transformation of the *cis*-diol *anti*-**443a** would be oxidation to give the corresponding dialdehyde **476** (**Scheme 139**). This could, for example, be condensed with an amine and reduced to access a chiral morpholine **477**. However, treatment of diol *anti*-**443a** with $NaIO_4$ in D_2O resulted in the rapid conversion of diol *anti*-**443a** to give a complex mixture of products by TLC and ^{1}H NMR spectroscopic analysis. The reaction

in MeOH-d_4 took 8 h to achieve 100% conversion of diol *anti*-**443a** but resulted in an analogous outcome. A possible explanation is that the hydrazone group was unstable in the presence of $NaIO_4$.



Scheme 139. Attempted oxidation of THF *anti*-443a using $NaIO_4$.

Another potentially useful transformation of hydrazone *anti*-**443a** would be conversion to cyclic sulfate **478** (**Scheme 140**). In principle this could then react with an external nucleophile in a regioselective fashion to give THF **480**.[256] However, treatment of hydrazone *anti*-**443a** with SO_2Cl_2 and NEt_3 in CH_2Cl_2 resulted in the rapid decomposition of *anti*-**443a** with no evidence for the target sulfate **478**. An alternative route to cyclic sulfates is *via* the corresponding cyclic sulfinate.[257] Treatment of THF *anti*-**443a** with $SOCl_2$ and NEt_3 in CH_2Cl_2 gave a compound consistent with target sulfinate **479** in 23% yield with minor impurities. [^{1}H NMR (600 MHz; $CDCl_3$) 5.80 (1H, d, J = 6.0, CH_2CHCH), 5.45 (1H, dd, J = 6.0, 4.1, CH_2CH)]. However, sulfinate **479** decomposed overnight at RT in a solution of $CDCl_3$. The relative stereochemistry of sulfinate **479** was not established.

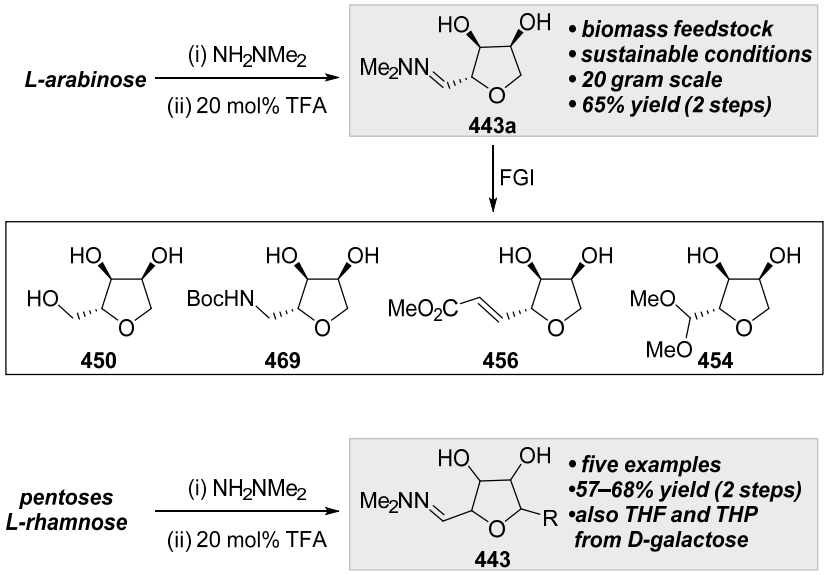


Scheme 140. Attempted synthesis of a cyclic sulfate 478.

4.3. Chapter IV Summary

In conclusion, a hydrazone-based methodology has been developed for the synthesis of chiral THFs from biomass feedstock under sustainable reaction conditions (**Scheme 141**). This approach was effective with different pentoses and L-rhamnose and was

demonstrated on a multi-gram scale. Furthermore, through reduction and hydrolysis of the hydrazone group, a diverse selection of chiral THFs were prepared without the use of protecting groups. This included a formal synthesis of 3*R*-3-hydroxymuscarine.



Scheme 141. Chapter IV Summary.

Chapter V. Conclusions and Future Work

5.1. Conclusions

In summary, this project has led to the successful development of novel methods to access a diverse range of medicinally relevant heterocycles (**Figure 24**). In Chapter II, conditions were developed for the regioselective cyclotrimerization of amide-tethered diynes and monoynes, which was applied to the synthesis of highly substituted isoindolinone products.[258] In Chapter III, the kinetically-controlled Diels–Alder reaction of 3-alkoxyfurans[190] and maleimides was developed for the synthesis of *endo*-cantharimides.[259] This Diels–Alder reaction was explored with the aid of computational calculations and the methodology extended to access a variety of sp^3-rich molecular scaffolds. In Chapter IV, a hydrazone-mediated cyclization of reducing sugars was developed for the synthesis of chiral THFs without the use of protecting groups.[260] Crucially, the environmental impact of this research has been reduced by using sustainable solvents and chemicals from biomass-derived feedstocks.

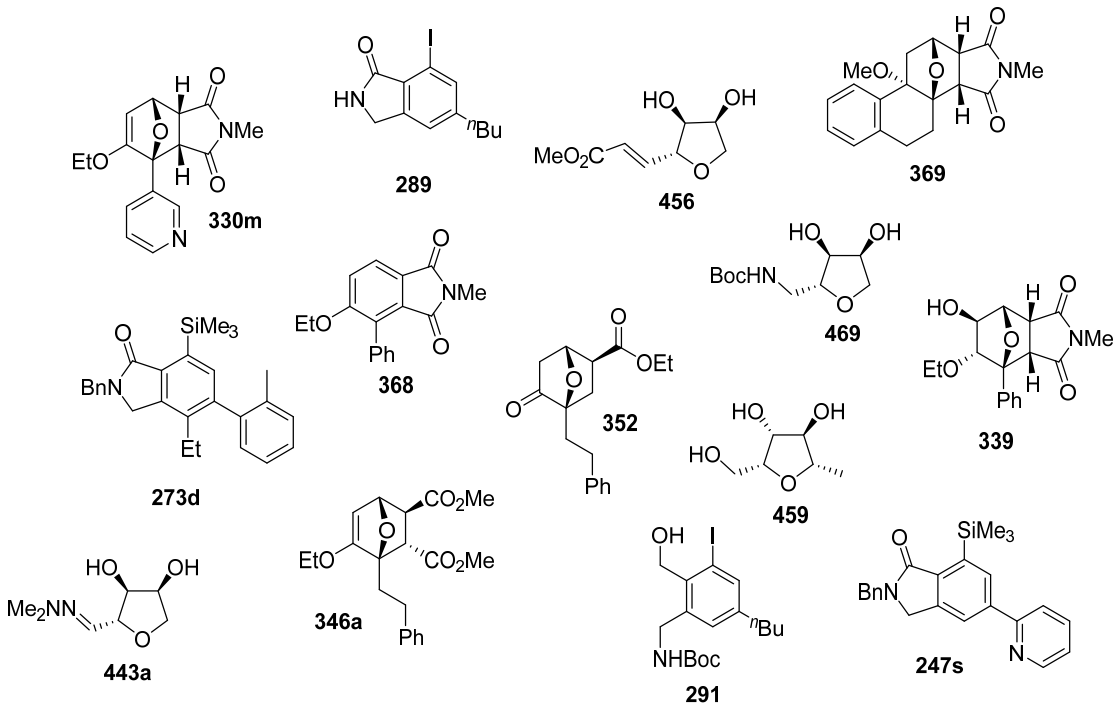
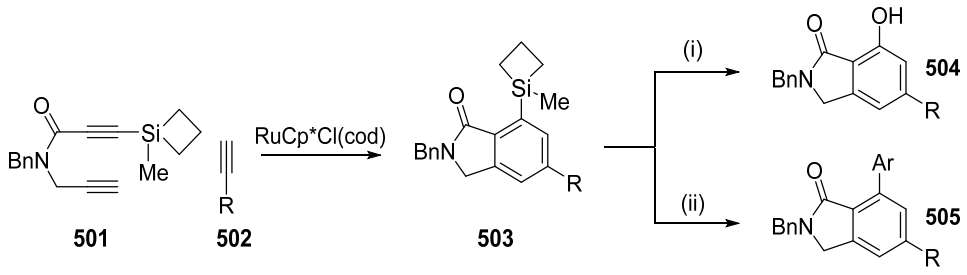


Figure 24. Summary of heterocycles prepared in Chapters II–IV.

5.2. Future Work

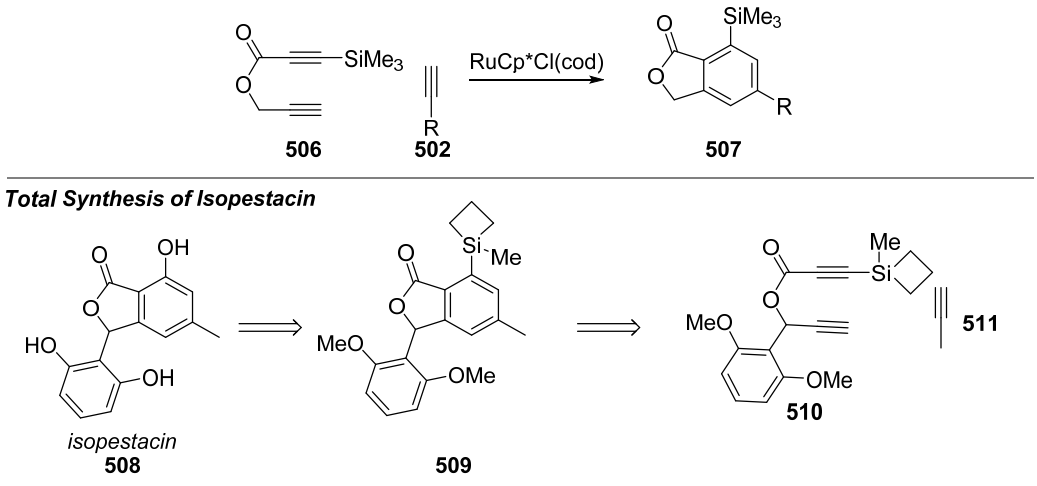
5.2.1. Alkyne Cyclotrimerizations

In Chapter II, the regioselectivity of alkyne cyclotrimerizations was generally controlled through use for a $SiMe_3$ regiodirecting group, which could then be substituted to prepare aryl halides. By investigating different directing groups new isoindolinones could be synthesized.[261] For example, a siletane directing group would give an isoindolinone that could in principle be oxidized to give phenol **504** (**Scheme 142**). [262] Aryl siletanes have also been used as the nucleophilic component of Hiyama-type cross-coupling reactions.[263]



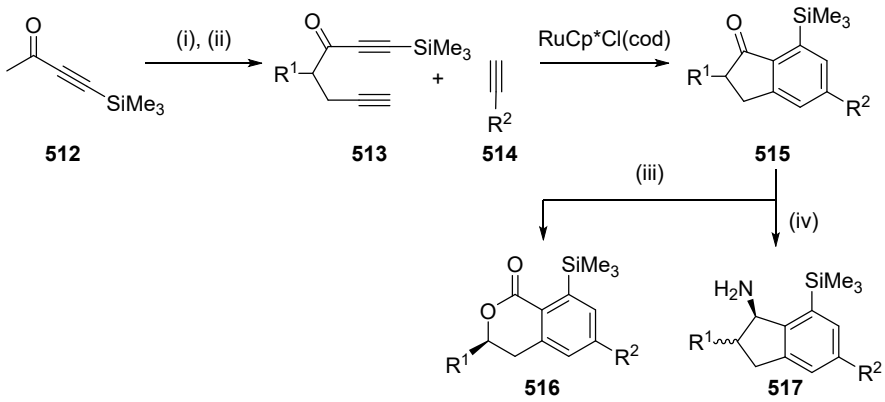
Scheme 142. Potential application of a siletanes directing group. Reagents and conditions: (i) H_2O_2, KF, $KHCO_3$; (ii) ArI, TBAF, $[allylPdCl]_2$, $P(^tBu)_3$.

An alternative to an amide-tethered diyne would be ester-tethered diyne **506**, which could be cyclized to form isobenzofuranone **508** (**Scheme 143**).[137] With different monoynes, this could be used to prepare a selection of aromatic products. The approach could also be applied to the total synthesis of isopestacin **508**,[264] a racemic natural product with antifungal activity.[265]



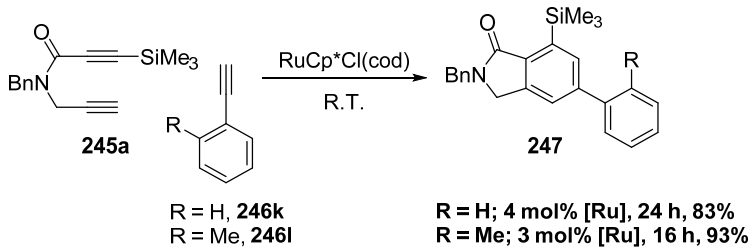
Scheme 143. Proposed cyclotrimerizations of ester-tethered diynes and monoynes.

The cyclization of ketone-tethered diynes would also be an interesting reaction to explore.[137] This class of diyne could be prepared by the selective alkylation of commercially available methyl ketone **512** (**Scheme 144**) and cyclized to generate different indanones **515**.[266] Indanone **515** could then be used as a substrate for a whole cell-catalyzed Baeyer–Villiger oxidation to prepare chiral lactone **516**.[267] If ketone **515** were racemized under the reaction conditions then lactone **516** could be prepared in an enantioconvergent fashion *via* a dynamic kinetic resolution. Alternatively, a transaminase could be used to convert ketone **515** into amine **517**.[268] If the transaminase was selective for the formation of one diastereoisomer over the other, this approach would also be an effective kinetic resolution strategy.



Scheme 144. Synthesizing substituted 1-indanones *via* an alkyne cyclotrimerization. Reagents and conditions: (i) LDA, R^1Br; (ii) LDA, propargyl bromide; (iii) cyclohexanone monooxygenase [see Ref 267], Lewatit MP62; (iv) (*R*)-ω-transaminase [see Ref 268].

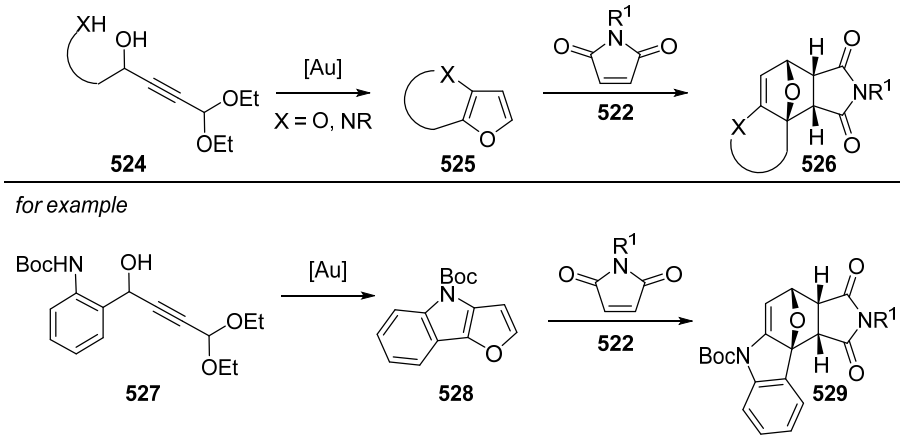
An interesting observation made in Chapter II was the unusual behaviour of 2-ethynyltoluene as a monoyne. The reaction of 2-ethynyltoluene and diyne **245a** occurred at a greater rate than the corresponding reaction of phenylacetylene and the reaction occurred with negligible diyne homo-coupling (**Scheme 145**). This reactivity could be explored further by considering the reaction of 2-ethylnytoluene with other diynes and by considering other 2-substituted phenylacetylenes. This phenomenon could also be explored with the aid of computational calculations.



Scheme 145. Unusual reactivity of 2-ethynyltoluene 246l.

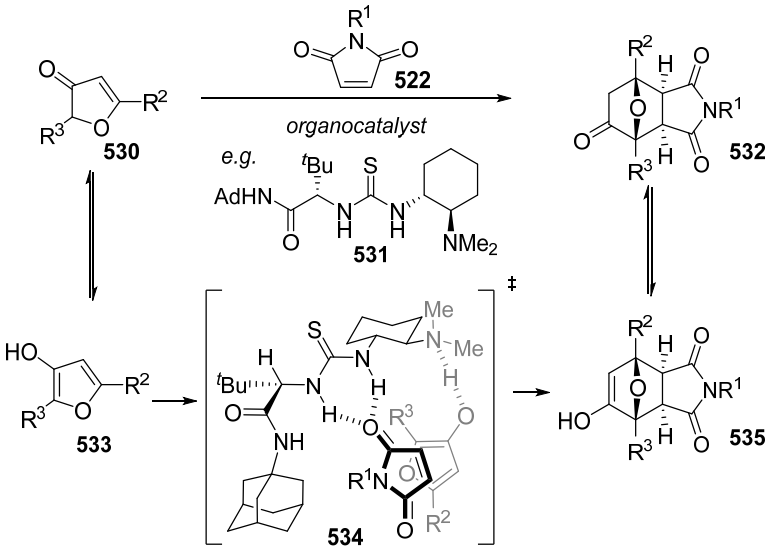
5.2.2. Furan-Diels–Alder Reactions

In Chapter III, *endo*-cantharimides were prepared from 2-substitued 3-alkoxyfurans. An alternative route to the *endo*-cantharimide could be *via* a fused bicyclic furan **525**, prepared from a propargylic alcohol with a pendent nucleophile **524** (**Scheme 146**). In principle a furan could be prepared using a pendent oxygen or nitrogen nucleophile, with the example of a carbamate nucleophile illustrated below. The Diels–Alder reactions of 3-aminofurans have not been widely explored.[269]



Scheme 146. Proposed synthesis of cantharimides from fused bicyclic furans.

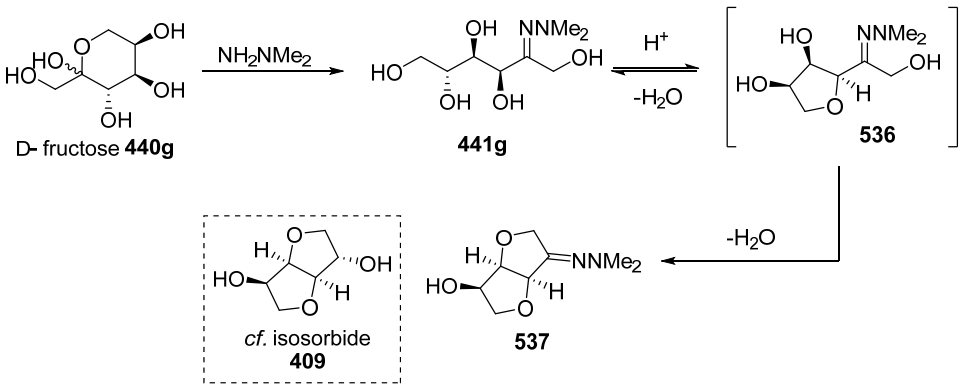
Another direction for further studies could be an asymmetric cantharimide synthesis. Manna and Mukherjee reported the organocatalytic asymmetric vinylogous Michael addition of maleimides and deconjugated butenolides[270] and a similar approach could be explored to prepare cantharimides (**Scheme 147**). Tautomerism of a substituted furanone[271] **530** would afford a 3-hydroxyfuran **533**, which could form a hydrogen bond with a chiral amine catalyst. If the same catalyst activated the maleimide through hydrogen bonding with a thiourea then it could catalyze the Diels–Alder reaction in an asymmetric fashion. Such a constrained transition state may also improve the diastereoselectivity of the reaction. The product of the Diels–Alder reaction would be enol **535**, which would tautomerize to give ketone product **532**. The cyclization of 3-alkoxyfurans and dienophiles using chiral Lewis acid catalysts could also be explored.[272]



Scheme 147. Proposed asymmetric synthesis of cantharimide 532.

5.2.3. Hydrazone-Mediated Transformations of Reducing Sugars

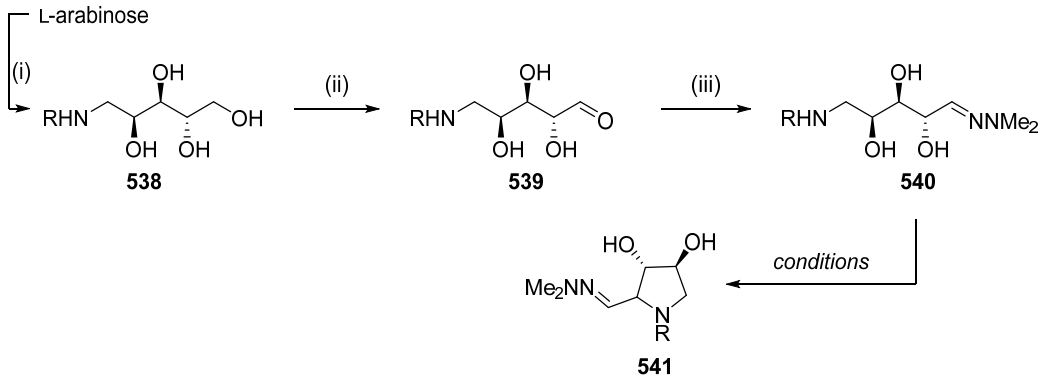
An interesting extension of the research in Chapter IV would be to prepare THFs from ketoses. For example, fructose-derived hydrazone **441g** may undergo a double condensation under acidic conditions to give isosorbide-derivative **537** (**Scheme 148**). The stereochemistry of the reaction would in principle be controlled by the reversible nature of the cyclization and the strong thermodynamic preference for *cis*-fused [5,5]-ring systems. As discussed in Chapter IV (**Section 4.2.4., Scheme 121**), a key challenge with this approach was the synthesis of hydrazone **441g**, which was not possible using the conditions used to prepare hydrazones from pentoses. This could potentially be addressed by exploring known literature conditions for related reactions,[273] such as Reeves' reported use of $B(OCH_2CF_3)_3$ to facilitate imine condensation.[274]



Scheme 148. Potential application of the hydrazone-methodology to ketoses.

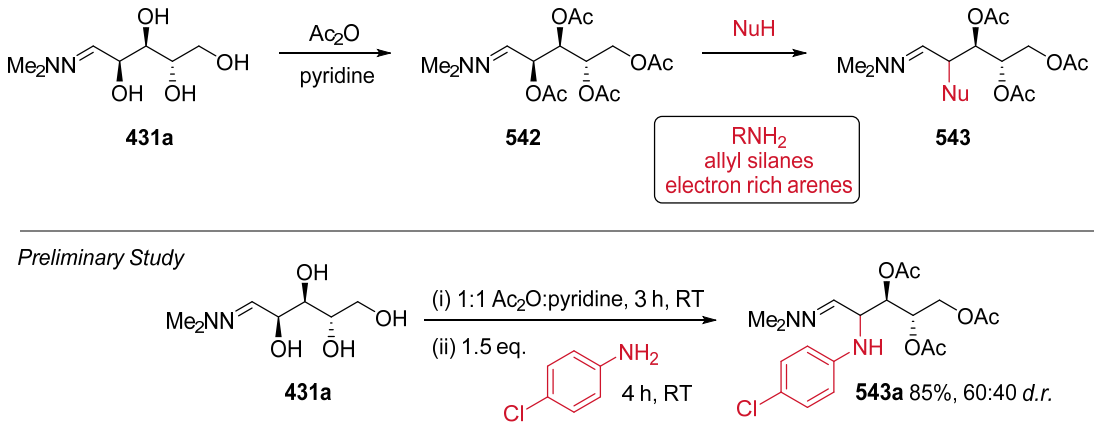
The optimized cyclization has primarily been applied to the synthesis of THFs. If it were possible to incorporate an internal nitrogen-based nucleophile the methodology could

potentially be applied to the synthesis of *N*-heterocyclic compounds (**Scheme 149**). A potential route into these compounds would be *via* amine **538**, formed from the reductive amination of L-arabinose. [275] A selective oxidation of the primary alcohol would give amino sugar **539**.[276] This could then be condensed with NH_2NMe_2 to generate hydrazone **540** and cyclization would give pyrrolidinone **541**. While a strong acid may be an inefficient catalyst for the cyclization of amines (given the propensity to form a salt in a polar solvent) the reaction could be more effective with a Lewis acid such as BF_3.THF. Using an electronically deactivated *N*-nucleophile (such as a carbamate) could also facilitate the cyclization. Another option would be to attempt a cyclization of hydrazone **540** under thermal conditions, without the use of a catalyst.



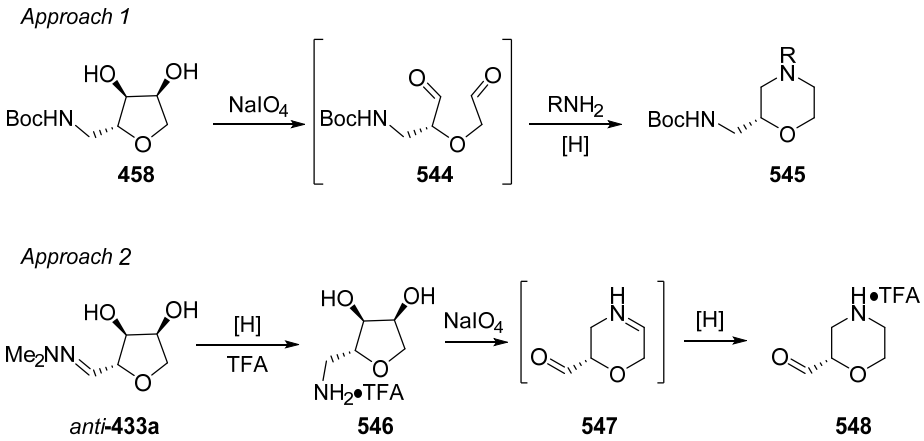
Scheme 149. Extending the methodology to *N*-heterocyclic compounds. Reagents and conditions: (i) RNH_2, $NaBH_3CN$, MeOH; (ii) TEMPO, trichloroisocyanuric acid, CH_2Cl_2 (iii) NH_2NMe_2, Amberlyst 15, MeOH.

Another potential area for further investigations would be the trapping of sugar-derived hydrazones with external nucleophiles. A potential method would be to transform arabinose-derived hydrazone **431a** into acylated product **542** (**Scheme 150**). The acylation would simultaneously deactivate the primary hydroxyl group as a nucleophile and activate the hydroxyl group adjacent to the hydrazone as a leaving group. In principle, this could be trapped out with a variety of nucleophiles to access a substituted carbohydrate derivative **543**. In a preliminary study, hydrazone **431a** was converted to the acylated product **542**. This compound was not stable enough to purify, but the crude product was concentrated and redissolved in MeOH before being treated with 4-chloroaniline. This gave a product consistent with hydrazone **543a** in 85% isolated yield as a 60:40 mixture of diastereoisomers.



Scheme 150. Proposed substitution of acylated hydrazone derivative 542 with external nucleophiles.

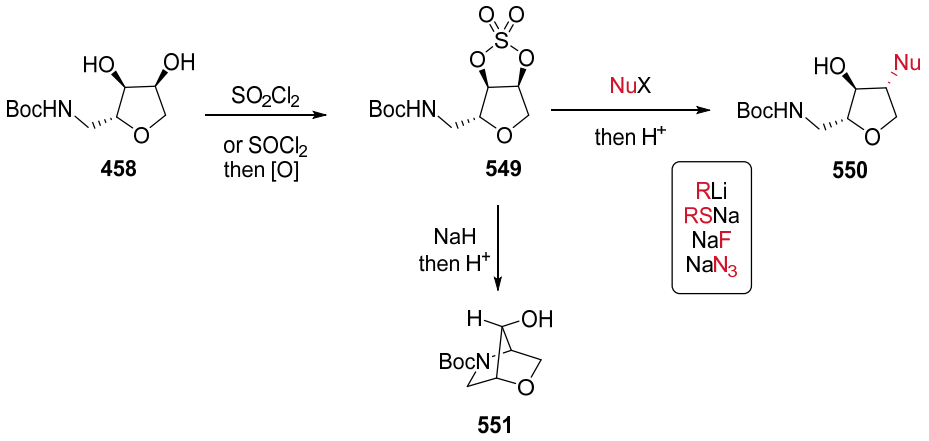
The oxidative ring-opening of diol *anti*-**433a** was briefly explored in Chapter IV (**Section 4.2.5., Scheme 139**) but generated a complex mixture, potentially due to oxidation of the hydrazone group. An alternative approach would be to oxidize carbamate **458** (which has been prepared as a single stereoisomer) to the corresponding dialdehyde **544**, and trap it out through a double-reductive amination to give chiral morpholine **545** (**Scheme 151**). An alternative approach would be to selectively oxidize ammonium salt **546**, which could be potentially prepared through reduction of hydrazone *anti*-**433a**. The corresponding dialdehyde could then condense with the pendent amine to give imine **547**, which could be selectively reduced to give morpholine **548**. A key challenge of this approach would be to avoid epimerization of the remaining stereocentre following oxidation.



Scheme 151. Potential route to chiral morpholines 545 and 548.

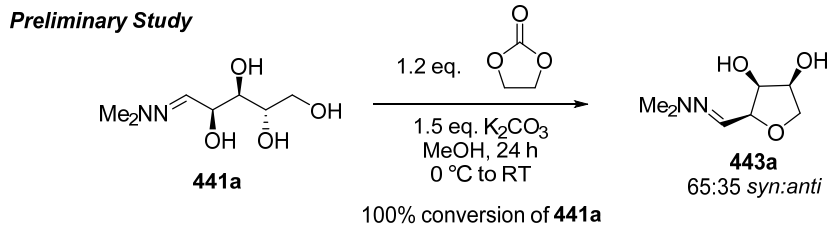
Another potentially valuable transformation for *cis*-diols prepared in Chapter IV would be selective displacement of one hydroxyl group with a nucleophile. The transformation of hydrazone *anti*-**433a** into a cyclic sulfate was briefly explored (**Section 4.2.5., Scheme 140**) but proved challenging, potentially due to the instability of the hydrazone group

under the reaction conditions. An alternative substrate could be carbamate **458**, which could be converted into cyclic sulfate **549** (**Scheme 152**). The cyclic sulfate could then be displaced with an external nucleophile to access a variety of chiral THFs **550** as single stereoisomers.[277] Ideally the regioselectivity of the cyclization would be controlled by the bulky carbamate sterically hindering attack of the proximal electrophilic centre. Alternatively, deprotonation of the carbamate using NaH would give an internal nucleophile, which could displace the cyclic sulfate to give ether **551**. The regioselectivity of this reaction would, in principle, be control by the kinetic preference for the formation of five-membered rings over four-membered rings.



Scheme 152. Application of cyclic sulfates.

A drawback of the optimized acid-mediated cyclization reaction is the need to use a strong acid as a catalyst, which has associated safety implications[278] and, as discussed above, potentially limits functional group compatibility. An attractive alternative would be to cyclize arabinose-derived hydrazone **401a** under basic conditions (**Scheme 153**). This was achieved in a preliminary study by using ethylene carbonate as an activating reagent. This gave THF **443a** with a preference for the *syn*-diastereoisomer, which is the opposite selectivity to that observed for the TFA-mediated cyclization.



Scheme 153. Proposed ethylene carbonate-mediated cyclization.

Chapter VI. Experimental Details

6.1. General Experimental

NMR spectra: ^{1}H and ^{13}C NMR spectra were recorded on Bruker AMX-300, Bruker AMX-400, Bruker Avance 400, Bruker Avance 500 or Brucker Avance 600 spectrometers. All chemical shifts are quoted in ppm relative to tetramethylsilane (δ = 0.00 ppm) and referenced to residual protonated solvent unless otherwise stated. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), combinations thereof or m (multiplet). All coupling constants (*J*) are quoted in Hz to 1 decimal place. The ^{13}C NMR spectra of novel compounds were assigned with the aid of HSQC NMR spectra.

Mass spectra: Mass spectra were obtained using either a VG70-SE or MAT 900XP spectrometer at the Department of Chemistry, University College London. High resolution values are quoted in Daltons to 4 decimal places and are within 5 ppm of their theoretical values.

Other data: Infrared spectra were recorded on a Perkin-Elmer 1605 Fourier transform spectrometer or a Perkin-Elmer spectrum 100 FT-IR spectrometer as thin films. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}) and are described as s (strong), m (medium) or w (weak) and where relevant br. (broad). Melting points were obtained using a Reichert hot-stage apparatus and are uncorrected. All optical rotation was measured on a Perkin-Elmer 343 polarimeter with a path length of 1 dm.

Chromatography: Analytical TLC was carried out using Merck Keiselgel aluminium-backed plates coated with silica gel, which were inspected under ultraviolet light and stained with basic potassium permanganate dip. Retention factors (R_f) are quoted with the solvent system in parentheses. Flash column chromatography was performed using BDH (40–60 μm) silica gel. Solvent systems are quoted in parentheses.

All experiments were conducted under an atmosphere of argon or nitrogen in oven-dried glassware. Solvent was used as commercially supplied unless otherwise stated.

6.2. General Experimental Procedures

General Amide Formation Procedure

Oxalyl chloride (1.1 eq.) was added dropwise to a stirring solution of acid **242** (1.2 eq.) and DMF (a few drops) in 2-MeTHF (0.85 mL/mmol of acid **242**) at RT. The reaction was stirred for 1 h before the crude acid chloride solution was added dropwise to a stirring solution of amine **244** (1.0 eq.) and NEt_3 (2.5 eq.) in 2-MeTHF (4.5 mL/mmol of amine **244**) at RT. The reaction was stirred for 1 h before being filtered through a silica plug, eluting with EtOAc. The filtrate was concentrated *in vacuo* to give the crude amide.

General Cyclization Procedure A- Cyclotrimerization of amide 245a and a Monoyne under Preliminary Conditions.

According to the modified procedure of Yamamoto *et al.*[137]: A solution of monoyne **246** (2.0 mmol) and RuCp*Cl(cod) (19 mg, 0.050 mmol, 10 mol%) in degassed CPME (2.0 mL) was added dropwise over 15 minutes to a stirring solution of amide **245a** (135 mg, 0.500 mmol) in degassed CPME (3.0 mL) at RT. The reaction was monitored by TLC and then the reaction mixture was filtered through a silica pad, eluting with EtOAc. The filtrate was concentrated *in vacuo* to give the crude isoindolinone product.

General Cyclization Procedure B- Cyclotrimerization of a Diyne and a Monoyne using a 3 h Dropwise Addition.

A solution of diyne (0.26 mmol) in CPME (1.6 mL) was added dropwise over 3 h to a stirring solution of monoyne (2.0 eq.) and RuCp*Cl(cod) in CPME (1.1 mL) at RT. The reaction was stirred for a specific period of time before the reaction mixture was filtered through a silica pad, eluting with EtOAc. The filtrate was concentrated *in vacuo* to give the crude isoindolinone product.

General Cyclization Procedure C- Cyclotrimerization of an Internal Diyne and a Monoyne using a 1 minute Dropwise Addition.

A solution of diyne (0.26 mmol) in CPME (1.6 mL) was added dropwise over 1 minute to a stirring solution of monoyne (2.0 eq.) and RuCp*Cl(cod) (10 mol%) in CPME (1.1 mL) at RT. The reaction was stirred for 24 h before the reaction mixture was filtered through a silica pad, eluting with EtOAc. The filtrate was concentrated *in vacuo* to give the crude isoindolinone product.

General Alkynylation Procedure: **Addition of 3,3-diethoxyprop-1-yne to Aldehydes**

According to the procedure of Sheppard *et al.*[190]: A solution of ^{n}BuLi (1.1 eq., 1.6 M in hexanes) was added dropwise to a stirring solution of 3,3-diethoxyprop-1-yne (1.2 eq.) in anhydrous THF (2.0 mL/mmol of aldehyde) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h before the aldehyde (1.0 eq.; neat unless otherwise indicated) was added dropwise. The reaction was stirred for 16 h, with the reaction allowed to slowly reach RT. The reaction was then cooled to 0 °C and was quenched by dropwise addition of aq. sat. NH_4Cl (20 mL). The reaction mixture was diluted with EtOAc (20 mL) and the aq. extract washed with EtOAc (3 × 20 mL). The combined organic extracts were dried (phase separator) and the filtrate was concentrated *in vacuo* to give the crude product.

General Furan Procedure: **Gold(I)-Catalyzed Cyclization of Propargylic Alcohols**

According to the modified Procedure of Sheppard *et al.*[190]: A solution of $[PPh_3AuNTf_2]_2PhMe$ (1 mol%, 2.0 mol% [Au]) in EtOH (50% of total volume) was added dropwise to a stirring solution of propargylic alcohol **316** in EtOH (50% of total volume) at RT to give a solution of the stated concentration. The resulting solution was stirred for 16 h before being purified by flash column chromatography (0 to 10% petrol 30–40 °C: TBME) to give the indicated 3-alkoxyfuran.

General Cycloaddition Procedure: **Catalyst-Free [4+2]-Cycloaddition**

A solution of dienophile (1.2 eq.) and 3-alkoxyfuran (1.0 eq.) in DMC (1.0 M with respect to the 3-alkoxyfuran) were stirred at RT until the reaction was judged to be complete by TLC or LC-MS analysis. The reaction was then diluted with EtOAc and loaded onto an aminopropyl cartridge. After 5 minutes the cartridge was then washed with EtOAc and the filtrate was concentrated *in vacuo* to give the indicated product.

General Hydrazone Synthesis Procedure

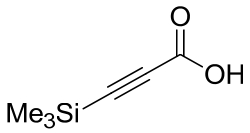
A stirring mixture of sugar **440** in MeOH (2.0 M) was treated with NH_2NMe_2 (2.0 eq.) and Amberlyst 15 (1.00 g/100 mmol sugar **440**) at RT. The resulting mixture was stirred at RT for 24 h before the mixture was filtered and the filtrate concentrated *in vacuo* to give the crude hydrazone.

General Acid-Catalyzed Cyclization Procedure

A stirring mixture of hydrazone **441** in MeOH (0.50 M) was treated with TFA (20 mol%) at RT and the reaction stirred at 40 °C for 16 h. The reaction was then quenched with aq. sat. $NaHCO_3$ and concentrated *in vacuo* to give the crude hydrazone.

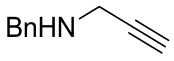
6.3. Compound Synthesis: Experimental Details & Compound Characterisation

3-(Trimethylsilyl)propiolic acid (242)[139]



According to the modified procedure of Fleming *et al.*[139]: A solution of ethynyltrimethylsilane (22 mL, 15 g, 150 mmol) in anhydrous THF (120 mL) was added slowly to a stirring solution of ethyl magnesium bromide (1.0 M in THF, 191 mL, 191 mmol) at 0 °C. The reaction mixture was stirred for 2 h at RT before being cooled to –20 °C. The solution was cautiously added to solid carbon dioxide (20 g, 450 mmol) and was stirred for 16 h, with the reaction allowed to slowly reach RT. The reaction was cooled to 0 °C and was quenched by dropwise addition of 1.0 M aq. HCl. The mixture was extracted with petrol 40–60 °C (4 × 100 mL), washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by vacuum distillation (b.p. 78–80 °C at 8 Torr) to the carboxylic acid **242** as a white crystalline solid (16.7 g, 117 mmol, 78%); m.p. 38–40 °C; b.p. 78–80 °C at 8 Torr (literature 108–100 °C at 10 Torr)[279]; R_f = 0.25 (1:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3000m br. (O-H), 2965s (C-H), 2181w (C≡C), 1691s (C=O), 1402m, 1254s, 919s, 847s; ^{1}H NMR (400 MHz; $CDCl_3$) 10.28 (1H, br. s, C(O)O*H*), 0.28 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) 157.5 (*C*O$_2$H), 97.5 (*C*≡C), 93.7 (*C*≡C), –1.0 (Si(*C*H$_3$)$_3$); data in accordance with the literature.[139]

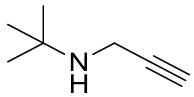
***N*-Benzylprop-2-yn-1-amine (244a)[140]**



According to the modified procedure of Burton and Hess[140]: Propargyl bromide (6.7 mL, 8.8 g, 80 wt. % in PhMe, 60 mmol) was added dropwise to benzylamine (40 mL, 39 g,

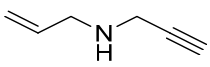
360 mmol) with continuous stirring at RT. The reaction was stirred for 16 h and then partitioned between 2.0 M aq. NaOH (50 mL) and Et_2O (50 mL). The aq. extract was washed with Et_2O (2 × 50 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by flash column chromatography (3:1 petrol 40–60 °C:EtOAc) to give the amine **244a** as a yellow oil (7.05 g, 48.6 mmol, 81%); R_f = 0.36 (3:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3292s (CC-H, N-H), 2838s (C-H), 1494s, 1453s; ^{1}H NMR (400 MHz; $CDCl_3$) 7.39–7.26 (5H, m, Ar*H*), 3.91 (2H, s, CH_2Ph), 3.46 (2H, d, *J* = 2.4, CH_2C≡C), 2.29 (1H, t, *J* = 2.4, C≡C*H*); ^{13}C NMR (100 MHz; $CDCl_3$) 139.4 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 127.2 (*Ar*), 82.1 (*C*≡C), 71.6 (*C*≡C), 52.3 (*C*H_2N), 37.4 (*C*H_2N); data in accordance with the literature.[140]

N-(*tert*-Butyl)prop-2-yn-1-amine (244c)[147]



According to the modified procedure of Sulpizo *et al*.[147]: Propargyl bromide (13 mL, 17 g, 80 wt. % in PhMe, 120 mmol) was added dropwise to a stirring solution of 2-methylpropan-2-amine (37 mL, 26 g, 350 mmol) in Et_2O (35 mL) at RT. The reaction was stirred at RT for 36 h before being concentrated *in vacuo*. The crude product was purified by distillation at atmospheric pressure (b.p. = 125–127 °C) to give the amine **244c** as a colorless oil (4.10 g, 79 wt. % with PhMe, 29 mmol, 24%); ν_{max} (film/cm^{-1}) 3306s (CC-H), 3245m br. (N-H), 2963s (C-H), 1476s; ^{1}H NMR (600 MHz; $CDCl_3$) 3.27 (2H, d, *J* = 2.3, CH_2N), 2.11 (1H, t, *J* = 2.3, CC*H*), 1.03 (9H, s, C(CH_3)$_3$); ^{13}C NMR (150 MHz; $CDCl_3$) 83.4 (*C*≡CH), 70.8 (C≡*C*H), 50.9 (*C*(CH$_3$)$_3$), 32.0 (*C*H_2N), 28.8 (C(*C*H$_3$)$_3$); data in accordance with the literature.[147]

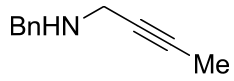
N-(Prop-2-ynyl)prop-2-en-1-amine (244d)[280]



According to the modified procedure of Li and Marks[148]: Propargyl chloride (6.8 mL, 7.0 g, 93 mmol) was added dropwise to allylamine (50 mL, 38 g, 660 mmol) with continuous stirring and the resulting solution was stirred at reflux for 48 h. The reaction mixture was allowed to cool to RT before being partitioned between water (300 mL) and Et_2O (300 mL). The aq. extract was washed with Et_2O (300 mL) and the combined

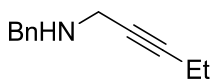
organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was distilled at atmospheric pressure (b.p. 126–128 °C) to give the-amine **244d** as a colorless oil (3.00 g, 31.5 mmol, 33%); b.p. 126–128 °C at atmospheric pressure (literature 44–46 °C at 0.22 Torr)[280]; ν_{max} (film/cm^{-1}) 3297s (CC-H) 3250m br. (N-H), 2832m (C-H), 1644s (C=C), 1452s; ^{1}H NMR (500 MHz; $CDCl_3$) 5.80–5.72 (1H, m, C*H*CH_2N), 5.10 (1H, dq, *J* = 17.3, 1.2, C*H*H=CH), 5.00 (1H, dq, *J* = 10.3, 1.2, CH*H*=CH), 3.30 (2H, d, *J* = 2.5, CH_2C≡C)), 3.21 (2H, dt, *J* = 6.1, 1.2, C=CHCH_2), 2.14 (1H, t, *J* = 2.5, C≡C*H*); ^{13}C NMR (125 MHz; $CDCl_3$) 135.9 (CH_2=*C*H), 116.6 (*C*H_2=CH), 82.0 (*C*≡C), 71.5 (*C*≡C), 50.8 (*C*H_2CH), 37.2 (*C*H_2C≡C); data in accordance with the literature.[280]

_N_-Benzylbut-2-yn-1-amine (244e)[281]



According to the modified procedure of Burton and Hess[140]: 1-Bromobut-2-yne (0.66 mL, 1.0 g, 7.5 mmol) was added dropwise to benzylamine (4.9 mL, 4.8 g, 45 mmol) with continuous stirring at 0 °C. The reaction was stirred for 16 h at RT and then partitioned between 1.0 M aq. NaOH (30 mL) and Et_2O (30 mL). The aq. extract was washed with Et_2O (2 × 30 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and the concentrated *in vacuo.* The crude product was purified by flash column chromatography (5:1 petrol 40–60 °C:EtOAc) to give the amine **244e** as a colorless oil (738 mg, 4.64 mmol, 62%); R_f = 0.38 (2:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3319m (N-H), 2917s (C-H), 1495s, 1453s; ^{1}H NMR (600 MHz; $CDCl_3$) 7.36–7.31 (4H, m, Ar*H*), 7.27–7.23 (1H, m, Ar*H*), 3.85 (2H, s, CH_2Ph), 3.38 (2H, q, *J* = 2.3, CH_2C≡C), 1.85 (3H, t, *J* = 2.3, CH_3), 1.51 (1H, br. s, N*H*); ^{13}C NMR (150 MHz; $CDCl_3$) 139.8 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 127.2 (*Ar*), 79.3 (*C*≡C), 77.3 (*C*≡C), 52.7 (Ph*C*H_2), 38.0 (*C*H_2C≡C), 3.7 (*C*H_3); data in accordance with the literature.[281]

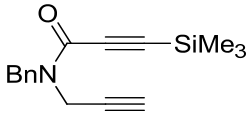
_N_-Benzylpent-2-yn-1-amine (244f)[140]



According to the modified procedure of Burton and Hess[140]: 1-bromopent-2-yne (0.72 mL, 1.0 g, 7.0 mmol) was added dropwise to benzylamine (4.5 mL, 4.5 g, 42 mmol) with continuous stirring at 0 °C. The reaction was stirred for 16 h at RT and then partitioned between 1.0 M aq. NaOH (30 mL) and Et_2O (30 mL). The aq. extract was

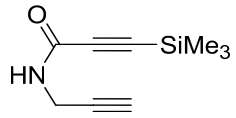
washed with Et_2O (2 × 30 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and the concentrated *in vacuo.* The crude product was purified by flash column chromatography (10:1 petrol 40–60 °C:EtOAc) to give the amine **244f** as a pale yellow oil (858 mg, 4.96 mmol, 71%); R_f = 0.24 (5:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3313w br. (N-H), 2975s (C-H), 1639s, 1453s; ^{1}H NMR (400 MHz; $CDCl_3$) 7.38–7.32 (4H, m, Ar*H*), 7.30–7.28 (1H, m, Ar*H*), 3.88 (2H, s, CH_2Ph), 3.42 (2H, t, *J* = 2.2, NCH_2C≡C), 2.25 (2H, qt, *J* = 7.5, 2.2, CH_2CH$_3$), 1.53 (1H, br. s, N*H*), 1.17, (3H, t, *J* = 7.5, *C*H$_3$); ^{13}C NMR (150 MHz; $CDCl_3$) 139.8 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 127.2 (*Ar*), 85.4 (*C*≡C), 77.4 (*C*≡C), 52.6 (*C*H$_2$Ph), 38.0 (N*C*H$_2$C≡C), 14.3 (*C*H$_3$), 12.6 (*C*H$_2$CH$_3$); data in accordance with the literature.[140]

_N_-Benzyl-_N_-(prop-2-yn-1-yl)-3-(trimethylsilyl)propiolamide (245a)



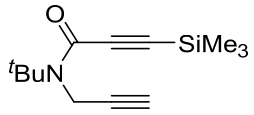
Prepared from amine **244a** (2.84 g, 19.6 mmol) according to the General Coupling Procedure and purified by flash column chromatography (9:1 petrol 40–60 °C:EtOAc) to give the *amide* **245a** as a yellow oil (4.48 g, 16.6 mmol, 85%); R_f = 0.44 (6:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3292m (CC-H), 2962m (C-H), 1634s (C=O), 1417s; ^{1}H NMR (400 MHz; $CDCl_3$) a mixture of rotamers R_1 (major) and R_2 (minor); 7.40–7.28 (5H, m, Ar*H* R_1; 5H, m, Ar*H* R_2), 4.93 (2H, s, CH_2Ph R_1), 4.74 (2H, s, CH_2Ph R_2), 4.27 (2H, d, *J* = 2.5, CH_2C≡C R_2), 4.12 (2H, d, *J* = 2.5, CH_2C≡C R_1), 2.35 (1H, t, *J* = 2.5, C≡C*H* R_2), 2.25 (1H, t, *J* = 2.5, C≡C*H* R_1), 0.25 (9H, s, Si(CH_3)$_3$ R_2), 0.22 (9H, s, Si(CH_3)$_3$ R_1); ^{13}C NMR (125 MHz; $CDCl_3$) a mixture of rotamers; 153.6 (*C*(O)), 153.5 (*C*(O)), 135.7 (*Ar*), 135.5 (*Ar*), 128.9 (*Ar*), 128.7 (*Ar*), 128.6 (*Ar*), 128.2 (*Ar*), 128.0 (*Ar*), 127.9 (*Ar*), 98.7 (*C*≡C), 98.5 (*C*≡C), 95.7 (*C*≡C), 95.3 (*C*≡C), 77.7 (*C*≡C), 77.6 (*C*≡C), 73.3 (*C*≡C), 72.6 (*C*≡C), 51.5 (*C*H$_2$N), 46.5 (*C*H$_2$N), 37.6 (*C*H$_2$C≡CH), 32.3 (*C*H$_2$C≡CH), –0.7 (Si(*C*H$_3$)$_3$), –0.8 (Si(*C*H$_3$)$_3$); HRMS (ESI$^+$) found [M+H]$^+$ 270.1308; $C_{16}H_{20}NOSi$ requires 270.1314.

N-(Prop-2-ynyl)-3-(trimethylsilyl)propiolamide (245b)



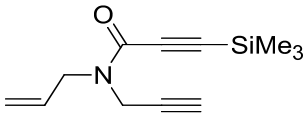
Prepared from propargylamine (0.34 mL, 0.29 g, 5.5 mmol) according to the General Coupling Procedure and purified by flash column chromatography (5:1 petrol 40–60 °C:EtOAc) to give the *amide* **245b** as a white crystalline solid (789 mg, 4.40 mmol, 80%); m.p. 42–44 °C; R_f = 0.38 (5:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3275s (CC-H and N-H), 2963m (C-H), 1638s (C=O), 1526s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 9.15 (1H, t, *J* = 5.3, N*H*), 3.85 (2H, dd, *J* = 5.3, 2.4, C*H*$_2$N), 3.13 (1H, t, *J* = 2.4, C≡C*H*), 0.21 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (125 MHz; DMSO-d$_6$) 151.4 (*C*(O)), 98.3 (*C*≡C), 90.5 (*C*≡C), 80.1 (*C*≡C), 73.3 (C≡*C*H), 28.1 (*C*H$_2$N), –0.8 (Si(*C*H$_3$)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 180.0847; C$_9$H$_{14}$NOSi requires 180.0847.

N-(*tert*-Butyl)-*N*-(prop-2-yn-1-yl)-3-(trimethylsilyl)propiolamide (245c)



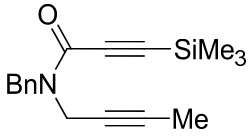
Prepared from amine **244c** (0.500 mg, 87 wt. % in PhMe, 3.9 mmol) according to the General Coupling Procedure and purified by flash column chromatography (12:1 petrol 40–60 °C:EtOAc) to give the *amide* **245c** as a white crystalline solid (612 mg, 2.6 mmol, 66%); m.p. 25–27 °C; R_f = 0.34 (12:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3252s (CC-H), 2965s (C-H), 1633s (C=O); ^{1}H NMR (600 MHz; DMSO-d$_6$) a mixture of rotamers R_1 (major) and R_2 (minor); 4.44 (2H, d, *J* = 0.5, C*H*$_2$N R_1), 4.23 (2H, br. s, C*H*$_2$N R_2), 3.35 (1H, t, *J* = 0.5, CC*H* R_1), 3.32 (1H, br. s, CC*H* R_2), 1.60 (9H, s, C(C*H*$_3$)$_3$ R_2), 1.42 (9H, s, C(C*H*$_3$)$_3$ R_1), 0.22 (9H, s, Si(C*H*$_3$)$_3$ R_1; 9H, s, Si(C*H*$_3$)$_3$ R_2); ^{13}C NMR (125 MHz; DMSO-d$_6$) 153.4 (*C*(O)), 97.9 (*C*≡C), 94.7 (*C*≡C), 80.9 (*C*≡C), 74.7 (H*C*≡C), 57.6 (*C*(CH$_3$)$_3$), 29.8 (*C*H$_2$N), 27.6 (C(*C*H$_3$)$_3$), –0.8 (Si(*C*H$_3$)$_3$); HRMS (ES$^+$) found [M+Na]$^+$ 258.1294; C$_{13}$H$_{21}$NNaOSi requires 258.1290.

_N_-Allyl-_N_-(prop-2-ynyl)-3-(trimethylsilyl)propiolamide (245d)



Prepared from amine **244d** (300 mg, 3.15 mmol) according to the General Coupling Procedure and purified by flash column chromatography (10:1 petrol 40–60 °C:EtOAc) to give the *amide* **245d** as a colorless oil (574 mg, 2.62 mmol, 83%); R_f = 0.43 (10:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3249m (CC-H), 2963m (C-H), 1632s (C=O), 1449s, 1411s; ^{1}H NMR (600 MHz; DMSO-d$_6$) a mixture of rotamers R_1 (major) and R_2 (minor); 5.90–5.83 (1H, m, C*H*=CH$_2$ R_1), 5.76–5.70 (1H, m, C*H*=CH$_2$ R_2), 5.24–5.16 (2H, m, CH=C*H*$_2$ R_1; 2H, m, CH=C*H*$_2$, R_2), 4.32 (2H, d, *J* = 2.4, C*H*$_2$C≡C R_2), 4.22 (2H, d, *J* = 5.7, NC*H*$_2$CH R_1), 4.11 (2H, d, *J* = 2.4, C*H*$_2$C≡C R_1), 3.99 (2H, d, *J* = 5.7, NC*H*$_2$CH R_2), 3.36 (1H, t, *J* = 2.4, C≡C*H* R_2), 3.23 (1H, t, *J* = 2.4, C≡C*H* R_1), 0.24 (9H, s, Si(C*H*$_3$)$_3$ R_2), 0.22 (9H, s, Si(C*H*$_3$)$_3$ R_1); ^{13}C NMR (125 MHz; DMSO-d$_6$) a mixture of rotamers 152.4 (*C*(O)), 152.3 (*C*(O)), 132.7 (*C*H=CH$_2$), 132.0 (*C*H=CH$_2$), 118.1 (CH=*C*H$_2$), 118.1 (CH=*C*H$_2$), 97.3 (*C*≡C), 96.9 (*C*≡C), 95.8 (*C*≡C), 95.7 (*C*≡C), 98.7 (*C*≡C), 98.6 (*C*≡C), 75.3 (C≡*C*H), 74.5 (C≡*C*H), 50.7 (N*C*H$_2$CH), 46.3 (N*C*H$_2$CH), 38.0 (*C*H$_2$C≡C), 33.2 (*C*H$_2$C≡C), –0.9 (Si(*C*H$_3$)$_3$), –0.9 (Si(*C*H$_3$)$_3$); HRMS (ES$^+$) found [M+H]$^+$ 220.1163; C$_{12}$H$_{18}$NOSi requires 220.1158.

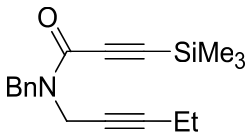
_N_-Benzyl-_N_-(but-2-yn-1-yl)-3-(trimethylsilyl)propiolamide (245e)



Prepared from amine **244e** (650 mg, 4.09 mmol) according to the General Coupling Procedure and purified by flash column chromatography (11:1 petrol 40–60 °C:EtOAc) to give the *amide* **245e** as a colorless oil (826 mg, 2.92 mmol, 71%); R_f = 0.31 (12:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2961s (C-H), 1631s (C=O), 1496s; ^{1}H NMR (500 MHz; DMSO-d$_6$) a mixture of rotamers R_1 (major) and R_2 (minor); 7.40–7.21 (5H, m, Ar*H* R_1; 5H, m, Ar*H* R_2), 4.81 (2H, s, PhC*H*$_2$ R_1), 4.56 (2H, s, PhC*H*$_2$ R_2), 4.25 (2H, q, *J* = 2.3, C*H*$_2$C≡C R_2), 4.01 (2H, q, *J* = 2.3, C*H*$_2$C≡C R_1), 1.77 (3H, t, *J* = 2.3, CC*H*$_3$ R_2), 1.74 (3H, t, *J* = 2.3, CC*H*$_3$ R_1), 0.22 (9H, s, Si(C*H*$_3$)$_3$ R_2), 0.17 (9H, s, Si(C*H*$_3$)$_3$ R_1); ^{13}C NMR (125 MHz; DMSO-d$_6$) a mixture of rotamers; 152.6 (*C*(O)), 152.5 (*C*(O)), 136.3 (*Ar*), 136.2 (*Ar*), 128.6 (*Ar*), 128.5 (*Ar*), 127.8 (*Ar*), 127.7 (*Ar*), 127.4 (*Ar*), 97.6

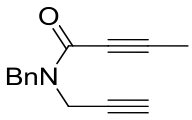
(*C*≡C), 97.3 (*C*≡C), 96.2 (*C*≡C), 95.8 (*C*≡C), 80.9 (*C*≡C), 80.0 (*C*≡C), 73.7 (*C*≡C), 73.6 (*C*≡C), 51.3 (*C*H_2Ph), 46.9 (*C*H_2Ph), 38.5 (*C*H_2C≡C), 33.4 (*C*H_2C≡C), 3.0 (C*C*H_3), 3.0 (C*C*H_3), –0.9 (Si(*C*H_3)$_3$), –1.0 (Si(*C*H_3)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 284.1459; $C_{17}H_{22}NOSi$ requires 284.1465.

_N_-Benzyl-_N_-(pent-2-yn-1-yl)-3-(trimethylsilyl)propiolamide (245f)



Prepared from amine **244f** (710 mg, 4.10 mmol) according to the General Coupling Procedure and purified by flash column chromatography (12:1 petrol 40–60 °C:EtOAc) to give the *amide* **245f** as a colorless oil (823 mg, 2.95 mmol, 72%); R_f = 0.39 (12:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2964s (C-H), 1632s (C=O), 1415s; ^{1}H NMR (600 MHz; DMSO-d_6) a mixture of rotamers R_1 (major) and R_2 (minor); 7.40–7.23 (5H, m, Ar*H* R_1; 5H, m, Ar*H* R_2), 4.82 (2H, s, PhC*H*$_2$ R_1), 4.57 (2H, s, PhC*H*$_2$ R_2), 4.28 (2H, t, *J* = 2.0, NC*H*$_2$C≡C R_2), 4.05 (2H, t, *J* = 2.0, NC*H*$_2$C≡C R_1), 2.18–2.11 (3H, m, C*H*$_2$CH$_3$ R_1; 3H, m, C*H*$_2$CH$_3$ R_2), 1.03–0.98 (3H, m, CH$_2$*C*H$_3$ R_1; 3H, m, CH$_2$*C*H$_3$ R_2), 0.24 (9H, s, Si(C*H*$_3$)$_3$ R_2), 0.18 (9H, s, Si(C*H*$_3$)$_3$ R_1); ^{13}C NMR (125 MHz; DMSO-d_6) a mixture of rotamers; 152.7 (*C*(O)), 152.5 (*C*(O)), 136.4 (*Ar*), 136.3 (*Ar*), 128.7 (*Ar*), 128.5 (*Ar*), 127.9 (*Ar*), 127.7 (*Ar*), 127.5 (*Ar*), 127.5 (*Ar*), 97.6 (*C*≡C), 97.4 (*C*≡C), 96.2 (*C*≡C), 95.8 (*C*≡C), 86.4 (*C*≡C), 85.7 (*C*≡C), 74.0 (*C*≡C), 73.8 (*C*≡C), 51.4 (*C*H$_2$Ph), 47.1 (*C*H$_2$Ph), 38.6 (N*C*H$_2$C≡C), 33.5 (N*C*H$_2$C≡C), 13.6 (CH$_2$*C*H$_3$), 11.6 (*C*H$_2$CH$_3$), 11.6 (*C*H$_2$CH$_3$), –0.9 (Si(*C*H$_3$)$_3$), –1.0 (Si(*C*H$_3$)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 298.1617; $C_{18}H_{24}NOSi$ requires 298.1622.

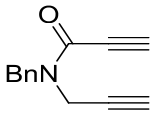
_N_-Benzyl-_N_-(prop-2-yn-1-yl)but-2-ynamide (245g)[137]



According to the modified procedure of Yamamoto *et al.*[137]: A solution of 2-butynoic acid (410 mg, 4.88 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was added dropwise to a stirring solution of amine **244a** (653 mg, 4.50 mmol), DMAP (62 mg, 0.51 mmol) and EDC (978 mg, 5.09 mmol) in anhydrous CH_2Cl_2 (8.6 mL) at 0 °C. The reaction was stirred for 16 h at RT before the reaction was partitioned between EtOAc (30 mL) and 1.0 M NaOH

(30 mL). The aq. extract was washed with EtOAc (3 × 30 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. This was dissolved in EtOAc (30 mL) and stirred with Amberlyst 15 (1.00 g) for 5 minutes. The mixture was then filtered and the resin washed with EtOAc (30 mL). The filtrate was concentrated *in vacuo* and purified by flash column chromatography (4:1 petrol 40–60 °C:EtOAc) to give the amide **245g** as a colorless oil (678 mg, 3.21 mmol, 71%); R_f = 0.28 (4:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3290s (CC-H), 2919w (C-H), 1624s (C=O), 1415s; ^{1}H NMR (600 MHz; DMSO-d_6) a mixture of rotamers R_1 (major) and R_2 (minor); 7.41–7.38 (2H, m, Ar*H* R_1/R_2), 7.36–7.27 (6H, m, Ar*H*, R_1/R_2), 7.24–7.21 (2H, m, Ar*H* R_1/R_2), 4.82 (2H, s, PhC*H*$_2$ R_1), 4.57 (2H, s, PhC*H*$_2$ R_2), 4.30 (2H, d, *J* = 2.4, C*H*$_2$C≡C R_2), 4.02 (2H, d, *J* = 2.4, C*H*$_2$C≡C R_1), 3.37 (1H, t, *J* = 2.4, C≡C*H* R_2), 3.22 (1H, t, *J* = 2.4, C≡C*H* R_1), 2.06 (3H, s, C*H*$_3$ R_2), 2.03 (3H, s, C*H*$_3$ R_1); ^{13}C NMR (125 MHz; DMSO-d_6) a mixture of rotamers; 153.5 (*C*(O)), 153.4 (*C*(O)), 136.3 (*Ar*), 136.2 (*Ar*), 128.8 (*Ar*), 128.6 (*Ar*), 127.8 (*Ar*), 127.8 (*Ar*), 127.5 (*Ar*), 127.5 (*Ar*), 90.7 (*C*≡C), 90.4 (*C*≡C), 78.7 (*C*≡C), 79.5 (*C*≡C), 75.6 (C≡*C*H), 74.7 (C≡*C*H), 72.8 (*C*≡C), 72.6 (*C*≡C), 51.2 (*C*H$_2$Ph), 46.8 (*C*H$_2$Ph), 38.0 (*C*H$_2$C≡C), 32.7 (*C*H$_2$C≡C), 3.5 (*C*H$_3$), 3.4 (*C*H$_3$); data in accordance with the literature.[137]

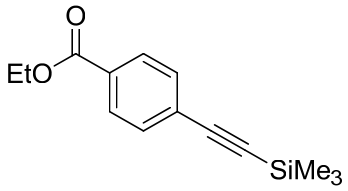
_N_-Benzyl-_N_-(prop-2-yn-1-yl)propiolamide (250)[282]



K_2CO_3 (14 mg, 0.10 mmol) was added to a stirring solution of amide **245a** (40 mg, 0.15 mmol) in MeOH (2.0 mL) at RT. The reaction was stirred for 10 minutes before being filtered through a silica plug, eluting with EtOAc. The filtrated was concentrated *in vacuo* and the crude product purified by flash column chromatography (3:1 petrol 40–60 °C:EtOAc) to give the amide **250** as a colorless oil (26 mg, 0.13 mmol, 90%); R_f = 0.21 (4:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3280s (CC-H), 2106s (C≡C), 1633s (C=O), 1449s, 1419s; ^{1}H NMR (600 MHz; DMSO-d_6) a mixture of rotamers R_1 (major) and R_2 (minor); 7.41–7.24 (5H, m, Ar*H* R_1; 5H, m, Ar*H* R_2), 4.85 (2H, s, PhC*H*$_2$ R_1), 4.72 (1H, s, *H*C≡CC(O) R_2), 4.67 (1H, s, *H*C≡CC(O) R_1), 4.59 (2H, s, PhC*H*$_2$ R_2), 4.32 (2H, d, *J* = 2.4, C*H*$_2$C≡C R_2), 4.06 (2H, d, *J* = 2.5, C*H*$_2$C≡C R_1), 3.19 (1H, t, *J* = 2.4, CH$_2$C≡C*H* R_2), 3.24 (1H, t, *J* = 2.5, CH$_2$C≡C*H* R_1); ^{13}C NMR (150 MHz; DMSO-d_6) a mixture of rotamers; 152.7 (*C*(O)), 152.6 (*C*(O)), 136.0 (*Ar*), 135.9 (*Ar*), 128.8 (*Ar*), 128.6 (*Ar*),

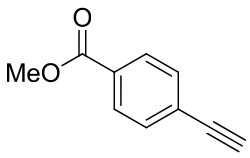
127.9 (*Ar*), 127.9 (*Ar*), 127.6 (*Ar*), 127.4 (*Ar*), 83.3 (*C*≡C), 83.0 (*C*≡C), 78.5 (*C*≡C), 78.2 (*C*≡C), 75.8 (*C*≡C), 75.5 (*C*≡C), 75.3 (*C*≡C), 74.9 (*C*≡C), 51.3 (*C*H_2Ph), 47.2 (*C*H_2Ph), 38.2 (*C*H_2C≡C), 33.1 (*C*H_2C≡C); data in agreement with the literature.[282]

Ethyl 4-((trimethylsilyl)ethynyl)benzoate (253)[283]



According to the modified procedure of Keana *et al.*[144]: Ethyl 4-iodobenzolate (0.43 mL, 700 mg, 2.5 mmol), ethynyltrimethylsilane (0.43 mL, 300 mg, 3.0 mmol), $Pd(PPh_3)_2Cl_2$ (53 mg, 0.075 mmol, 3.0 mol%) and CuI (29 mg, 0.15 mmol, 6.0 mol%) were added to a stirring degassed solution of NEt_3 (1.3 mL, 0.94 g, 9.3 mmol) in THF (5.0 mL) in a sealed tube. The reaction mixture was stirred at 80 °C for 2 h before it was allowed to cool to RT. The reaction mixture was filtered and the residue washed with EtOAc. The filtrate was concentrated *in vacuo* and the crude product was purified by flash column chromatography (40:1 petrol 40–60 °C:EtOAc) to give the ester **253** as a white crystalline solid (615 mg, 3.00 mmol, 100%); m.p. 24–26 °C (literature 30 °C)[283]; R_f = 0.29 (40:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2961s (C-H), 2159s (C≡C), 1718s (C=O), 1605s; ^{1}H NMR (600 MHz; DMSO-d_6) 7.98–7.95 (2H, m, Ar*H*), 7.52–7.49 (2H, m, Ar*H*), 4.36 (2H, q, *J* = 7.2, CH_2O), 1.38 (3H, t, *J* = 7.2, CH_3CH_2), 0.26 (9H, s, Si(CH_3)$_3$); ^{13}C NMR (125 MHz; DMSO-d_6) 166.1 (*C*(O)), 131.9 (*Ar*), 130.1 (*Ar*), 129.4 (*Ar*), 127.7 (*Ar*), 104.2 (*C*≡C), 97.6 (*C*≡C), 61.2 (*C*H_2O), 14.4 (*C*H_3CH_2), –0.1 (Si(*C*H_3)$_3$); data in accordance with the literature.[283]

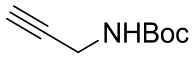
Methyl 4-ethynylbenzoate (246e)[284]



K_2CO_3 (345 mg, 0.250 mmol) was added to a stirring solution of ester **253** (615 mg, 2.50 mmol) in MeOH (5.0 mL) at RT. The suspension was stirred for 30 minutes before the reaction mixture was filtered through a silica plug, eluting with EtOAc. The filtrate was concentrated *in vacuo* and the crude product was purified by flash column

chromatography (40:1 petrol 40–60 °C:EtOAc) to give the ester **246e** as a white crystalline solid (366 mg, 2.28 mmol, 92%); m.p. 80–82 °C (literature 87–88 °C)[284]; R_f = 0.26 (40:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3242s (CC-H), 2952m (C-H), 1700s (C=O), 1607s, 1434s; ^{1}H NMR (600 MHz; DMSO-d_6) 7.94 (2H, d, *J* = 8.3, Ar*H*), 7.61 (2H, d, *J* = 8.3, Ar*H*), 4.49 (1H, s, CC*H*), 3.85 (3H, s, CH_3O); ^{13}C NMR (150 MHz; DMSO-d_6) 165.6 (*C*(O)), 132.1 (*Ar*), 129.6 (*Ar*), 129.5 (*Ar*), 126.5 (*Ar*), 84.0 (C*C*H), 82.6 (*C*CH), 52.4 (*C*H$_3$O); data in accordance with the literature.[283]

tert-Butyl prop-2-yn-1-ylcarbamate (246f)[145]



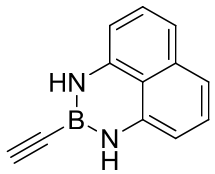
According to the modified procedure of Molander and Cadoret[145]: Boc_2O (7.50 g, 34.4 mmol) was added portionwise to a stirring solution of propargylamine (2.2 mL, 1.9 g, 34 mmol) in CH_2Cl_2 (60 mL) at RT. The reaction mixture was stirred at RT for 1 h before it was concentrated *in vacuo* to give the crude product, which was purified by recrystallization (Et_2O/hexane) to give the amine **246f** as an off-white crystalline solid (4.98 g, 32.1 mmol, 93%); m.p. 32–34 °C (literature 41–42 °C)[145]; R_f = 0.29 (12:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3306s (CC-H or N-H), 3281s (CC-H or N-H), 2980s (C-H), 1809m, 1682s (C=O); ^{1}H NMR (500 MHz; $CDCl_3$) 4.85–4.69 (1H, br. s, N*H*), 3.92–3.81 (2H, br. s, CH_2N), 2.20 (1H, t, *J* = 2.5, C≡C*H*), 1.43 (9H, s, C(CH_3)$_3$); ^{13}C NMR (500 MHz; $CDCl_3$) 155 (*C*(O)), 80.2 (*C*≡C), 80.2 (*C*Me$_3$), 71.3 (*C*≡C), 30.4 (*C*H$_2$N), 28.4 (C(*C*H$_3$)$_3$); data in accordance with the literature.[145]

2,2,5,5,8,8-Hexamethyl-3,7-dioxa-2,8-disilanonane (256)[146]

According to the procedure of Vaultier *et al.*[146]: 2-dimethylpropane-1,3-diol (5.00 g, 48.0 mmol) was added portionwise to a stirring mixture of NH(SiMe$_3$)$_2$ (10 mL, 7.7 g, 48 mmol) and Me$_3$SiCl (1.2 mL, 1.0 g, 9.6 mmol) at RT. The reaction was heated to 70 °C for 2 h before being allowed to cool to RT. Water (50 mL) and Et_2O (50 mL) were added to the reaction mixture and the aq. layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the silyl ether **256** as a colorless oil (10.0 g, 40.7 mmol, 84%); R_f = 0.66 (100:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2957s (C-H), 1476m; ^{1}H NMR (500 MHz; $CDCl_3$) 3.28 (4H, s, CH_2O), 0.80 (6H, s, C(CH_3)$_2$), 0.08 (18H, Si(CH_3)$_3$); ^{13}C NMR (125 MHz; $CDCl_3$)

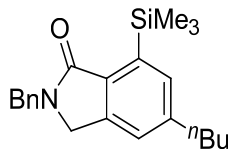
67.9 (*C*H_2O), 37.2 (*C*(CH_3)$_2$), 21.4 (C(*C*H_3)$_2$), –0.5 (Si(*C*H_3)$_3$); data in accordance with the literature.[146]

2-Ethynyl-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborinine (246g)[129b]



According to the modified procedure of Gandon *et al.*[129b]: Silyl ether **256** (4.46 g, 17.9 mmol) and Me_3SiCl (4.6 mL, 3.9 g, 36 mmol), were added dropwise to a stirring solution of potassium ethynyltrifluoroborate (2.50 g, 95% purity, 17.5 mmol) in anhydrous acetone (22 mL) at RT. The reaction was stirred at RT for 20 h before the reaction mixture was filtered and the filtrate concentrated *in vacuo*. The crude intermediate was dissolved in PhMe (300 mL) and 1,8-diaminonapthaline (2.06 g, 13.0 mmol) was added portionwise to the stirring solution at RT. The reaction was heated at reflux for 24 h before it was allowed to cool to RT. The reaction was concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (6:1 petrol 40–60 °C:EtOAc) to give the boramide **246g** as a white crystalline solid (0.950 g, 4.95 mmol, 38%); m.p. 87–89 °C (literature 92 °C)[129b]; R_f = 0.26 (40:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3426s (N-H), 3405s (N-H), 3241s (CC-H), 2076s (C≡C), 1595s, 1500s, 1403s; ^{1}H NMR (600 MHz; DMSO-d_6) 8.30 (2H, s, N*H*), 7.03 (2H, t, *J* = 8.1, Ar*H*), 6.88 (2H, d, *J* = 8.1, Ar*H*), 6.42 (2H, d, *J* = 8.1, Ar*H*), 3.42 (1H, s, C≡C*H*); ^{13}C NMR (150 MHz; DMSO-d_6) 141.7 (*Ar*), 135.9 (*Ar*), 127.6 (*Ar*), 119.9 (*Ar*), 116.7 (*Ar*), 105.5 (*Ar*), 94.1 (H*C*≡C), 85.4 (br., B*C*≡C); data in accordance with the literature.[129b]

2-Benzyl-5-butyl-7-(trimethylsilyl)isoindolin-1-one (247a)

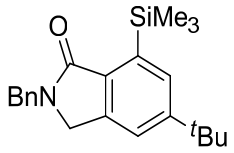


Prepared from amide **245a** and 1-hexyne according to General Cyclization Procedure A (crude ratio **247a**:**8a** = 2:1) and purified by flash column chromatography (16:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247a** (107 mg, 0.304 mmol, 61%).

Prepared from amide **245a**, 1-hexyne and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio **247a**:**248a** = 9:1) and purified by flash column chromatography (13:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247a** (75 mg, 0.21 mmol, 81%).

The *isoindolinone* **247a** was isolated as a colorless oil; R_f = 0.36 (6:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2955m (C-H), 2930m (C-H), 1688s (C=O), 1454m, 1409m; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.34–7.21 (7H, m, Ar*H*), 4.68 (2H, s, C*H*$_2$N), 4.24 (2H, s, C*H*$_2$N), 2.60 (2H, t, *J* = 7.7, ArC*H*$_2$CH$_2$), 1.51 (2H, m, ArCH$_2$C*H*$_2$), 1.26 (2H, m, C*H*$_2$CH$_3$), 0.83 (3H, t, *J* = 7.4, CH$_2$C*H*$_3$), 0.34 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (125 MHz; DMSO-d$_6$) 168.5 (*C*(O)), 144.8 (*Ar*), 142.1 (*Ar*), 137.7 (*Ar*), 136.9 (*Ar*), 134.3 (*Ar*), 134.0 (*Ar*), 128.6 (*Ar*), 127.6 (*Ar*), 127.2 (*Ar*), 123.7 (*Ar*), 48.9 (*C*H$_2$N), 45.4 (*C*H$_2$N), 35.1 (Ar*C*H$_2$CH$_2$), 33.2 (ArCH$_2$*C*H$_2$), 21.8 (*C*H$_2$CH$_3$), 13.7 (CH$_2$*C*H$_3$), –0.4 (Si(*C*H$_3$)$_3$); HRMS (EI$^+$) found [M]$^+$ 351.2011; $C_{22}H_{29}NOSi$ requires 351.2013.

2-Benzyl-5-(*tert*-butyl)-7-(trimethylsilyl)isoindolin-1-one (247b)



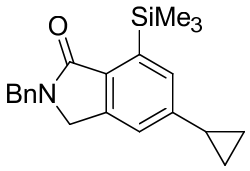
Prepared from 3,3-dimethyl-1-butyne according to General Cyclization Procedure A (crude ratio **247b**:**258a** = 1:3) and purified by flash column chromatography (12:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247b** (38 mg, 0.11 mmol, 22%).

Prepared from amide **245a**, 3,3-dimethyl-1-butyne and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio **247b**:**248a** = 2:1) and purified by flash column chromatography (12:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247b** (60 mg, 0.17 mmol, 65%).

The *isoindolinone* **247b** was isolated as a white crystalline solid; m.p. 100–102 °C; R_f = 0.31 (12:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2958s (C-H), 1689s (C=O), 1598m, 1410s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 8.00 (1H, s, Ar*H*), 7.97 (1H, s, Ar*H*), 7.77–7.73 (2H, m, Ar*H*), 7.69–7.66 (3H, m, Ar*H*), 5.13 (2H, s, C*H*$_2$N), 4.72 (2H, s, C*H*$_2$N), 1.71 (9H, s, C(C*H*$_3$)$_3$), 0.79 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (125 MHz; DMSO-d$_6$) 168.8 (*C*(O)), 153.2 (*Ar*), 142.4 (*Ar*), 138.1 (*Ar*), 136.8 (*Ar*), 134.5 (*Ar*), 130.9 (*Ar*), 129.0 (*Ar*), 128.0 (*Ar*), 127.6 (*Ar*), 121.5 (*Ar*), 49.5 (*C*H$_2$N), 45.7 (*C*H$_2$N), 31.5 (*C*Me$_3$), 29.5

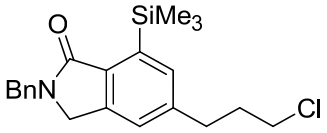
(C(*C*H$_3$)$_3$), 0.0 (Si(*C*H$_3$)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 352.2093; $C_{22}H_{30}NOSi$ requires 352.2097.

2-Benzyl-5-cyclopropyl-7-(trimethylsilyl)isoindolin-1-one (247h)



Prepared from amide **245a**, cyclopropyl acetylene and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio **247h**:**248a** = 10:1) and purified by flash column chromatography (13:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247h** as a white crystalline solid (72 mg, 0.21 mmol, 81%); m.p. 66–68 °C; R_f = 0.31 (13:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2951s (C-H), 1686s (C=O), 1600m, 1454s, 1410s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.35–7.23 (6H, m, Ar*H*), 7.13 (1H, s, Ar*H*), 4.69 (2H, s, C*H*$_2$N), 4.25 (2H, s, C*H*$_2$N), 2.03–1.98 (1H, m, C*H*(CH$_2$)$_2$), 1.00–0.97 (2H, m, CH(C*H*H')$_2$), 0.73–0.69 (2H, m, CH(CH*H*')$_2$), 0.35 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.5 (*C*(O)), 146.5 (*Ar*), 142.3 (*Ar*), 137.7 (*Ar*), 136.7 (*Ar*), 134.0 (*Ar*), 131.9 (*Ar*), 128.7 (*Ar*), 127.6 (*Ar*), 127.3 (*Ar*), 120.0 (*Ar*), 48.9 (*C*H$_2$N), 45.4 (*C*H$_2$N), 15.5 (*C*H(CH$_2$)$_2$), 10.1 (CH(*C*H$_2$)$_2$), –0.4 (Si(*C*H$_3$)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 336.1784; $C_{21}H_{26}NOSi$ requires 336.1784.

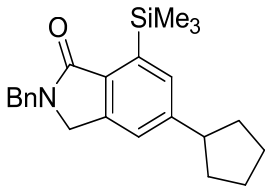
2-Benzyl-5-(3-chloropropyl)-7-(trimethylsilyl)isoindolin-1-one (247i)



Prepared from amide **245a**, 5-chloro-1-pentyne and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio **247i**:**248a** = 9:1) and purified by flash column chromatography (12:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247i** as a colorless oil (81 mg, 0.22 mmol, 83%); R_f = 0.31 (12:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2951s (C-H), 1684s (C=O), 1600m, 1453s, 1409s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.40 (1H, s, Ar*H*), 7.36 (1H, s, Ar*H*), 7.35–7.32 (2H, m, Ar*H*), 7.30–7.24 (3H, m, Ar*H*), 4.70 (2H, s, C*H*$_2$N), 4.29 (2H, s, C*H*$_2$N), 3.61 (2H, t, *J* = 6.5, C*H*$_2$Cl), 2.78 (2H, t, *J* = 7.6, C*H*$_2$CH$_2$CH$_2$Cl), 2.01 (2H, m, C*H*$_2$CH$_2$Cl), 0.36 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.4 (*C*(O)), 143.3 (*Ar*), 142.3 (*Ar*),

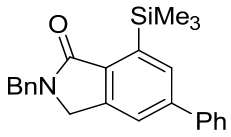
137.7 (*Ar*), 137.1 (*Ar*), 134.7 (*Ar*), 134.2 (*Ar*), 128.7 (*Ar*), 128.5 (*Ar*), 127.3 (*Ar*), 125.1 (*Ar*), 49.0 (*C*H_2N), 45.4 (*C*H_2N), 44.7 (*C*H_2Cl), 33.8 (*C*$H_2$$CH_2$Cl), 32.5 (*C*$H_2$$CH_2$$CH_2$Cl), –0.4 (Si(*C*$H_3$)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 372.1548; $C_{21}H_{27}ClNOSi$ requires 372.1550.

2-Benzyl-5-cyclopentyl-7-(trimethylsilyl)isoindolin-1-one (247j)



Prepared from amide **245a**, cyclopentyl acetylene and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio **247j**:**248a** = 6:1) and purified by flash column chromatography (15:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247j** as a colorless oil (78 mg, 0.21 mmol, 81%); R_f = 0.43 (15:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2951s (C-H), 1686s (C=O), 1599m, 1453s, 1409s; ^{1}H NMR (600 MHz; DMSO-d_6) 7.45–7.23 (7H, m, Ar*H*), 4.70 (2H, s, C*H*$_2$N), 4.28 (2H, s, C*H*$_2$N), 3.06–3.00 (1H, m, C*H*(CH$_2$)$_2$), 2.03–1.98 (2H, m, CHC*H*H'), 1.78–1.72 (2H, m, CHCH$_2$C*H*H'), 1.66–1.59 (2H, m, CHCH$_2$CH*H*'), 1.56–1.49 (2H, m, CHCH*H*'), 0.35 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d_6) 168.5 (*C*(O)), 148.6 (*Ar*), 142.2 (*Ar*), 137.7 (*Ar*), 136.8 (*Ar*), 134.5 (*Ar*), 133.0 (*Ar*), 128.7 (*Ar*), 127.6 (*Ar*), 127.3 (*Ar*), 122.4 (*Ar*), 49.0 (*C*H_2N), 45.6 (*C*H(CH$_2$)$_2$), 45.4 (*C*H_2N), 34.5 (CH(*C*H_2)$_2$), 25.1 (CHCH$_2$*C*H_2), –0.4 (Si(*C*H_3)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 364.2091; $C_{23}H_{30}NOSi$ requires 364.2097.

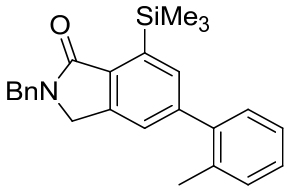
2-Benzyl-5-phenyl-7-(trimethylsilyl)isoindolin-1-one (247k)



Prepared from amide **245a**, phenylacetylene and RuCp*Cl(cod) (4 mg, 4 mol%) over 24 h according to General Cyclization Procedure B (crude ratio **247k**:**248a** = 6:1) and purified by flash column chromatography (15:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247k** as a white crystalline solid (81 mg, 0.22 mmol, 83%); R_f = 0.25 (15:1 petrol 40–60 °C:EtOAc); m.p. 117–119 °C; ν_{max} (film/cm^{-1}) 2950s (C-H), 1687s (C=O), 1597m, 1454s, 1409s; ^{1}H NMR (600 MHz; DMSO-d_6) 7.80 (1H, s, Ar*H*), 7.75 (1H, d, *J* = 1.3, Ar*H*), 7.69–7.66 (2H, m, Ar*H*), 7.50 (2H, t, *J* = 4.8, Ar*H*), 7.42–7.35 (3H, m, Ar*H*), 7.30–

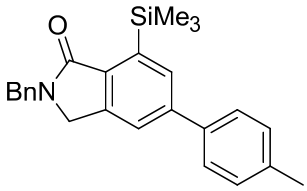
7.27 (3H, m, Ar*H*), 4.75 (2H, s, CH_2N), 4.40 (2H, s, CH_2N), 0.41 (9H, s, Si(CH_3)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.3 (*C*(O)), 142.7 (*Ar*), 142.2 (*Ar*), 140.1 (*Ar*), 137.8 (*Ar*), 137.6 (*Ar*), 135.7 (*Ar*), 132.6 (*Ar*), 129.1 (*Ar*), 128.8 (*Ar*), 128.0 (*Ar*), 127.7 (*Ar*), 127.4 (*Ar*), 127.2 (*Ar*), 127.8 (*Ar*), 49.2 (*C*H$_2$N), 45.5 (*C*H$_2$N), –0.4 (Si(*C*H$_3$)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 372.1779; $C_{24}H_{26}NOSi$ requires 372.1784.

2-Benzyl-5-*o*-tolyl-7-(trimethylsilyl)isoindolin-1-one (247l)



Prepared from amide **245a**, 1-ethynyl-2-methylbenzene and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio **247l**:**248a** >10:1) and purified by flash column chromatography (17:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247l** as a colorless oil (95 mg, 0.25 mmol, 93%); R_f = 0.28 (17:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2956s (C-H), 1689s (C=O), 1598m, 1454s, 1410s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.52 (1H, s, Ar*H*), 7.45 (1H, s, Ar*H*), 7.38–7.21 (9H, m, Ar*H*), 4.74 (2H, s, CH_2N), 4.38 (2H, s, CH_2N), 2.22 (3H, s, ArCH_3), 0.38 (9H, s, Si(CH_3)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.3 (*C*(O)), 143.1 (*Ar*), 142.0 (*Ar*), 140.9 (*Ar*), 137.6 (*Ar*), 136.9 (*Ar*), 135.3 (*Ar*), 134.7 (*Ar*), 134.6 (*Ar*), 130.5 (*Ar*), 129.6 (*Ar*), 128.8 (*Ar*), 127.8 (*Ar*), 127.7 (*Ar*), 127.4 (*Ar*), 126.1 (*Ar*), 124.8 (*Ar*), 49.2 (*C*H$_2$N), 45.5 (*C*H$_2$N), 20.2 (Ar*C*H$_3$), –0.4 (Si(*C*H$_3$)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 386.1939; $C_{25}H_{28}NOSi$ requires 386.1935.

2-Benzyl-5-(*p*-tolyl)-7-(trimethylsilyl)isoindolin-1-one (247c)

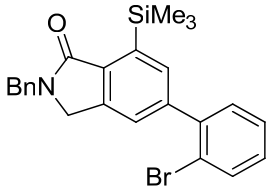


Prepared from 4-ethynyltoluene according to General Cyclization Procedure A (crude ratio **247c**:**248a** = 2:1) and purified by flash column chromatography (6:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247c** (82 mg, 0.21 mmol, 42%).

Prepared from amide **245a**, 4-ethynyltoluene and RuCp*Cl(cod) (4 mg, 4 mol%) over 24 h according to General Cyclization Procedure B (crude ratio **247c**:**248a** = 6:1) and purified by flash column chromatography (15:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247c** (82 mg, 0.22 mmol, 81%).

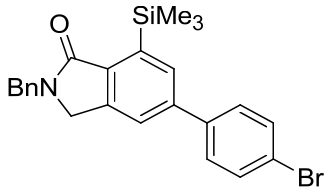
The *isoindolinone* **247c** was isolated as a white crystalline solid; R_f = 0.50 (6:1 petrol 40–60 °C:EtOAc); m.p. 78–80 °C; ν_{max} (film/cm^{-1}) 2950s (C-H), 1686s (C=O), 1453s, 1409s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.76 (1H, s, Ar*H*), 7.73–7.72 (1H, m, Ar*H*), 7.58–7.56 (2H, m, Ar*H*), 7.38–7.34 (2H, m, Ar*H*), 7.30–7.27 (5H, m, Ar*H*), 4.74 (2H, s, C*H*$_2$N), 4.38 (2H, s, C*H*$_2$N), 2.34 (3H, s, ArC*H*$_3$), 0.40 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.3 (*C*(O)), 142.7 (*Ar*), 142.1 (*Ar*), 137.7 (*Ar*), 137.6 (*Ar*), 137.4 (*Ar*), 137.1 (*Ar*), 135.4 (*Ar*), 132.3 (*Ar*), 129.7 (*Ar*), 128.8 (*Ar*), 127.7 (*Ar*), 127.3 (*Ar*), 127.0 (*Ar*), 122.4 (*Ar*), 49.2 (*C*H$_2$N), 45.5 (*C*H$_2$N), 20.7 (Ar*C*H$_3$), –0.4 (Si(*C*H$_3$)$_3$); HRMS (ESI$^+$) found [M-Me]$^+$ 370.1620; $C_{24}H_{24}NOSi$ requires 370.1627.

2-Benzyl-5-(2-bromophenyl)-7-(trimethylsilyl)isoindolin-1-one (247m)



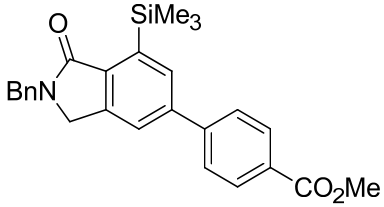
Prepared from amide **245a**, 1-ethynyl-2-methylbenzene and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio **247m**:**248a** = 8:1) and purified by flash column chromatography (20:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247m** as a colorless oil (95 mg, 0.21 mmol, 80%); R_f = 0.37 (15:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2974s (C-H), 1688s (C=O), 1602m, 1452s, 1409s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.74 (1H, dd, *J* = 8.0, 0.8, Ar*H*), 7.56 (2H, d, *J* = 2.9, Ar*H*), 7.47–7.45 (1H, m, Ar*H*), 7.42–7.40 (1H, m, Ar*H*), 7.37–7.26 (6H, m, Ar*H*), 4.75 (2H, s, C*H*$_2$N), 4.38 (2H, s, C*H*$_2$N), 0.38 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.2 (*C*(O)), 142.1 (*Ar*), 141.8 (*Ar*), 141.4 (*Ar*), 137.6 (*Ar*), 136.7 (*Ar*), 135.9 (*Ar*), 134.9 (*Ar*), 133.2, (*Ar*), 131.5 (*Ar*), 129.8 (*Ar*), 128.7 (*Ar*), 128.2 (*Ar*), 127.8 (*Ar*), 127.4 (*Ar*), 125.0 (*Ar*), 121.6 (*Ar*), 49.2 (*C*H$_2$N), 45.5 (*C*H$_2$N), –0.4 (Si(*C*H$_3$)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 450.0870; $C_{24}H_{25}{}^{79}BrNOSi$ requires 450.0889.

2-benzyl-5-(4-bromophenyl)-7-(trimethylsilyl)isoindolin-1-one (247n)



Prepared from amide **245a**, 1-ethynyl-2-methylbenzene and RuCp*Cl(cod) (3 mg, 3 mol%) over 24 h according to General Cyclization Procedure B (crude ratio **247n**:**248a** = 5:1) and purified by flash column chromatography (12:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247n** as a colorless oil (98 mg, 0.22 mmol, 83%); R_f = 0.20 (15:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2950s (C-H), 1684s (C=O), 1600s, 1495s, 1453s, 1409s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.77 (1H, s, Ar*H*), 7.72 (1H, s, Ar*H*), 7.29–7.26 (3H, m, Ar*H*), 7.37–7.33 (2H, m, Ar*H*), 7.66–7.60 (4H, m, Ar*H*), 4.74 (2H, s, CH_2N), 4.37 (2H, s, CH_2N), 0.40 (9H, s, Si(CH_3)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.2 (*C*(O)), 142.7 (*Ar*), 140.8 (*Ar*), 139.2 (*Ar*), 137.9 (*Ar*), 137.6.9 (*Ar*), 136.0 (*Ar*), 132.4 (*Ar*), 132.0 (*Ar*), 129.3 (*Ar*), 128.7 (*Ar*), 127.7 (*Ar*), 127.4 (*Ar*), 122.6 (*Ar*), 121.6 (*Ar*), 49.2 (*C*H$_2$N), 46.2 (*C*H$_2$N), –0.4 (Si(*C*H$_3$)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 450.0877; C$_{24}$H$_{25}$^{79}BrNOSi requires 450.0889.

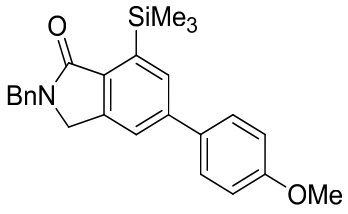
Methyl 4-(2-benzyl-1-oxo-7-(trimethylsilyl)isoindolin-5-yl)benzoate (247e)



Prepared from amide **245a**, methyl 4-ethynylbenzoate **246e** and RuCp*Cl(cod) (3 mg, 3 mol%) over 24 h according to General Cyclization Procedure B (crude ratio **247e**:**248a** = 5:1) and purified by flash column chromatography (15:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247e** as a colorless oil (89 mg, 0.21 mmol, 79%); R_f = 0.29 (9:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2951s (C-H), 1720s (ester C=O) 1686s (lactam C=O), 1608s, 1434s, 1410s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 8.05 (1H, s, Ar*H*), 8.03 (1H, s, Ar*H*), 7.83–7.77 (4H, m, Ar*H*), 7.36–7.32 (2H, m, Ar*H*), 7.29–7.26 (3H, m, Ar*H*), 4.73 (2H, s, CH_2N), 4.37 (2H, s, CH_2N), 3.89 (3H, s, OCH_3)), 0.41 (9H, s, Si(CH_3)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.1 (*C*(O)), 166.0 (*C*(O)), 144.5 (*Ar*), 142.7 (*Ar*), 140.8 (*Ar*), 138.0 (*Ar*), 137.5 (*Ar*), 136.5 (*Ar*), 132.7 (*Ar*), 129.9 (*Ar*), 128.9

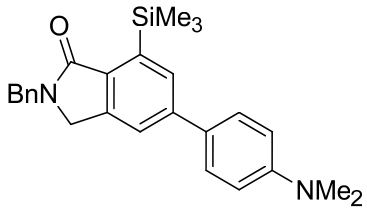
(*Ar*), 128.7 (*Ar*), 127.7 (*Ar*), 127.5 (*Ar*), 127.4 (*Ar*), 123.1 (*Ar*), 52.2 (O*C*H$_3$), 49.2 (*C*H$_2$N), 45.5 (*C*H$_2$N), –0.4 (Si(*C*H$_3$)$_3$); HRMS (ES$^+$) found [M+Na]$^+$ 452.1642; $C_{26}H_{27}NNaO_3Si$ requires 452.1658.

2-Benzyl-5-(4-methoxyphenyl)-7-(trimethylsilyl)isoindolin-1-one (247o)



Prepared from amide **245a**, 1-ethynyl-4-methoxybenzene and RuCp*Cl(cod) (5 mg, 5 mol%) over 24 h according to General Cyclization Procedure B (crude ratio **247o**:**248a** = 6:1) and purified by flash column chromatography (12:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247o** (83 mg, 0.21 mmol, 79%) as a colorless oil; R_f = 0.28 (15:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2952s (C-H), 1685s (C=O), 1606s 1516s, 1454s, 1409s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.73 (1H, s, Ar*H*), 7.71 (1H, s, Ar*H*), 7.61 (2H, d, *J* = 8.7, Ar*H*), 7.36–7.33 (2H, m, Ar*H*), 7.28–7.26 (3H, m, Ar*H*), 7.04 (2H, d, *J* = 8.7 Ar*H*), 4.72 (2H, s, C*H*$_2$N), 4.35 (2H, s, C*H*$_2$N), 3.78 (3H, s, OC*H*$_3$), 0.40 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.4 (*C*(O)), 159.3 (*Ar*), 142.7 (*Ar*), 141.8 (*Ar*), 137.6 (*Ar*), 137.6 (*Ar*), 135.0 (*Ar*), 132.3 (*Ar*), 132.1 (*Ar*), 128.7 (*Ar*), 128.3 (*Ar*), 127.7 (*Ar*), 127.4 (*Ar*), 122.1 (*Ar*), 114.5 (*Ar*), 55.2 (OC*H*$_3$), 49.1 (C*H*$_2$N), 45.5 (C*H*$_2$N), –0.4 (Si(*C*H$_3$)$_3$); HRMS (ES$^+$) found [M+Na]$^+$ 424.1694; $C_{25}H_{27}NNaO_2Si$ requires 424.1709.

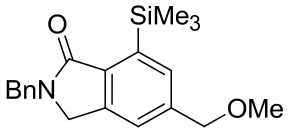
2-Benzyl-5-(4-(dimethylamino)phenyl)-7-(trimethylsilyl)isoindolin-1-one (247p)



Prepared from amide **245a**, 4-ethynyl-*N*,*N*-dimethylaniline and RuCp*Cl(cod) (10 mg, 10 mol%) over 24 h according to General Cyclization Procedure B (crude ratio **247p**:**248a** = 7:1) and purified by flash column chromatography (10:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247p** (86 mg, 0.21 mmol, 79%) as a colorless oil; R_f = 0.27 (10:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2897s (C-H), 1682s (C=O),

1609s, 1592s 1526s, 1452s, 1409s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.70 (2H, s, Ar*H*), 7.53 (2H, d, *J* = 8.8, Ar*H*), 7.37–7.34 (2H, m, Ar*H*), 7.30–7.26 (3H, m, Ar*H*), 6.81 (2H, d, *J* = 8.8, Ar*H*), 4.72 (2H, s, C*H*$_2$N), 4.35 (2H, s, C*H*$_2$N), 2.93 (6H, s, N(C*H*$_3$)$_2$)), 0.40 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.5 (*C*(O)), 150.2 (*Ar*), 142.7 (*Ar*), 142.3 (*Ar*), 137.7 (*Ar*), 137.4 (*Ar*), 134.2 (*Ar*), 131.4 (*Ar*), 128.7 (*Ar*), 127.7 (*Ar*), 127.7 (*Ar*), 127.4 (*Ar*), 127.1 (*Ar*), 121.2 (*Ar*), 112.7 (*Ar*), 49.2 (*C*H$_2$N), 45.5 (*C*H$_2$N), 39.9 (N(*C*H$_3$)$_2$), –0.3 (Si(*C*H$_3$)$_3$); HRMS (ES$^+$) found [M+H]$^+$ 415.2219; $C_{26}H_{31}N_2OSi$ requires 415.2206.

2-Benzyl-5-(methoxymethyl)-7-(trimethylsilyl)isoindolin-1-one (247d)

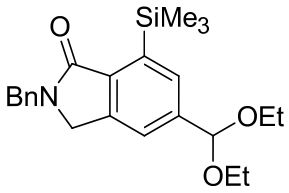


Prepared from 3-methoxy-1-propyne according to General Cyclization Procedure A (crude ratio **247d**:**248a** = 2:1) and purified by flash column chromatography (6:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247d** (79 mg, 0.23 mmol, 47%).

Prepared from amide **245a**, 3-methoxy-1-propyne and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio **247d**:**248a** = 3:2) and purified by flash column chromatography (12:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247d** (50 mg, 0.15 mmol, 56%).

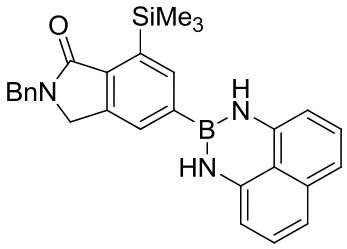
The *isoindolinone* **247d** was isolated as a white crystalline solid; m.p. 57–59 °C; R_f = 0.26 (12:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2896s (C-H), 1684s (C=O), 1453s, 1409s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.48 (s, 2H, Ar*H*), 7.37–7.33 (2H, m, Ar*H*), 7.29–7.26 (3H, m, Ar*H*), 4.71 (2H, s, C*H*$_2$N), 4.49 (2H, s, C*H*$_2$O), 4.33 (2H, s, C*H*$_2$N), 3.31 (3H, s, OC*H*$_3$), 0.36 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.4 (*C*(O)), 142.1 (*Ar*), 140.7 (*Ar*), 137.6 (*Ar*), 137.0 (*Ar*), 135.9 (*Ar*), 132.9 (*Ar*), 128.7 (*Ar*), 127.7 (*Ar*), 127.4 (*Ar*), 123.1 (*Ar*), 73.5 (*C*H$_2$O), 57.8 (O*C*H$_3$), 49.1 (*C*H$_2$N), 45.5 (*C*H$_2$N), –0.4 Si(*C*H$_3$)$_3$); HRMS (ESI$^+$) found [M]$^+$ 339.1647; $C_{20}H_{25}NO_2Si$ requires 339.1649.

2-Benzyl-5-(diethoxymethyl)-7-(trimethylsilyl)isoindolin-1-one (247q)



Prepared from amide **245a**, 3,3-diethoxyprop-1-yne and RuCp*Cl(cod) (3 mg, 3 mol%) over 24 h according to General Cyclization Procedure B (crude ratio **247q**:**248a** = 0.8:1) and purified by flash column chromatography (17:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247q** (45 mg, 0.11 mmol, 43%) as a colorless oil; R_f = 0.27 (17:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2874s (C-H), 1689s (C=O), 1454s, 1409s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.59 (1H, s, Ar*H*), 7.57 (1H, s, Ar*H*), 7.37–7.26 (5H, m, Ar*H*), 5.56 (1H, s, C*H*(OEt)$_2$), 4.72 (2H, s, C*H*$_2$N), 4.36 (2H, s, C*H*$_2$N), 3.59–3.53 (2H, m, OC*H*H'), 3.32–3.46 (2H, m, OCH*H*'), 1.14 (6H, t, *J* = 7.0, CH$_2$C*H*$_3$), 0.36 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.3 (*C*(O)), 141.9 (*Ar*), 141.3 (*Ar*), 137.6 (*Ar*), 136.8 (*Ar*), 136.6 (*Ar*), 132.0 (*Ar*), 128.7 (*Ar*), 127.7 (*Ar*), 127.4 (*Ar*), 122.4 (*Ar*), 100.9 (*C*H(OEt)$_2$), 61.1 (O*C*H$_2$), 49.2 (*C*H$_2$N), 45.5 (*C*H$_2$N), 15.2 (CH$_2$*C*H$_3$), –0.4 (Si(*C*H$_3$)$_3$); HRMS (ES$^+$) found [M+Na]$^+$ 420.1970; $C_{23}H_{31}NNaO_3Si$ requires 420.1971.

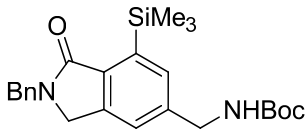
2-Benzyl-5-(1*H*-naphtho[1,8-de][1,3,2]diazaborinin-2(3*H*)-yl)-7-(trimethylsilyl)isoindolin-1-one (247g)



Prepared from amide **245a**, boramide **246g** and RuCp*Cl(cod) (5 mg, 5 mol%) over 24 h according to General Cyclization Procedure B (crude ratio **247g**:**248a** = 3:1) and purified by flash column chromatography (3:1 petrol 40–60 °C: Et$_2$O) to give the *isoindolinone* **247g** as a white crystalline solid (67 mg, 0.15 mmol, 55%); m.p. 96–98 °C; R_f = 0.56 (2:3 petrol 40–60 °C: Et$_2$O); ν_{max} (film/cm^{-1}) 3333s (N-H), 2952s (C-H), 1672s (C=O), 1599s, 1512s, 1405s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 8.35 (2H, s, N*H*), 8.02 (1H, s, Ar*H*), 7.96 (1H, s, Ar*H*), 7.39–7.36 (2H, m, Ar*H*), 7.31–7.28 (3H, m, Ar*H*), 7.09 (2H, t, *J* = 8.0, Ar*H*), 6.91 (2H, d, *J* = 8.0, Ar*H*) 6.59 (2H, d, *J* = 7.2, Ar*H*), 4.76 (2H, s, C*H*$_2$N), 4.42

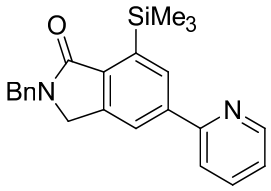
(2H, s, C*H*$_2$N), 0.44 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.6 (*C*(O)), 142.3 (*Ar*), 140.8 (*Ar*), 138.0 (*Ar*), 137.9 (*Ar*), 137.7 (*Ar*), 136.0 (*Ar*), 136.0 (*Ar*), 128.8 (*Ar*), 128.4 (*Ar*), 127.7 (*Ar*), 127.7 (*Ar*), 127.4 (*Ar*), 119.8 (*Ar*), 116.4 (*Ar*), 105.8 (*Ar*), 49.2 (*C*H$_2$N), 45.5 (*C*H$_2$N), –0.1 (Si(*C*H$_3$)$_3$), N$_2$B*C* not observed; HRMS (EI$^+$) found [M]$^+$ 461.2089; C$_{28}$H$_{28}$BN$_3$OSi requires 461.2089.

tert-Butyl ((2-benzyl-1-oxo-7-(trimethylsilyl)isoindolin-5-yl)methyl)carbamate (247f)



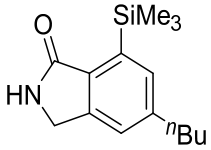
Prepared from amide **245a**, carbamate **246f** and RuCp*Cl(cod) (5 mg, 5 mol%) over 24 h according to General Cyclization Procedure B (crude ratio **247f**:**248a** = 2:1) and purified by flash column chromatography (8:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **247f** as a white crystalline solid (71 mg, 0.17 mmol, 63%); m.p. 124–126 °C; R_f = 0.44 (4:1 petrol 40–60 °C: Et$_2$O); ν_{max} (film/cm^{-1}) 3334s (N-H), 2975s (C-H), 1685s (lactam and carbamate C=O), 1516s, 1454s, 1411s; ^{1}H NMR (600 MHz; DMSO-d$_6$) a mixture of rotamers R$_1$ (major) and R$_2$ (minor) 7.51–7.45 (2H, m, Ar*H*, N*H* R$_1$; 2H, m, Ar*H*, N*H* R$_2$), 7.38–7.34 (3H, m, Ar*H* R$_1$; 3H, m, Ar*H* R$_2$), 7.30–7.24 (3H, m, Ar*H* R$_1$; 3H, m, Ar*H* R$_2$), 4.71 (2H, s, C*H*$_2$NCH$_2$ R$_1$; 2H, s, C*H*$_2$NCH$_2$ R$_2$), 4.32 (2H, s, C*H*$_2$NCH$_2$ R$_1$; 2H, s, C*H*$_2$NCH$_2$ R$_2$), 4.20 (2H, s, *J* = 6.2, C*H*$_2$NH R$_1$) 4.13 (2H, br. s, C*H*$_2$NH R$_2$) 1.39 (9H, s, C(C*H*$_3$)$_3$ R$_1$), 1.29 (9H, s, C(C*H*$_3$)$_3$ R$_2$), 0.35 (9H, s, Si(C*H*$_3$)$_3$ R$_1$; 9H, s, Si(C*H*$_3$)$_3$ R$_2$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.4 (lactam *C*(O)), 155.9 (carbamate *C*(O)), 142.7 (*Ar*), 142.1 (*Ar*), 137.7 (*Ar*), 136.9 (*Ar*), 135.2 (*Ar*), 132.6 (*Ar*), 128.7 (*Ar*), 127.7 (*Ar*), 127.3 (*Ar*), 122.6 (*Ar*), 77.9 (*C*(CH$_3$)$_3$), 49.1 (*C*H$_2$NCH$_2$), 45.5 (*C*H$_2$NCH$_2$), 43.5 (*C*H$_2$NH), 28.3 (*C*Me$_3$), –0.4 (Si(*C*H$_3$)$_3$); HRMS (ES$^+$) found [M+H]$^+$ 425.2274; C$_{24}$H$_{33}$N$_2$O$_3$Si requires 425.2260.

2-Benzyl-5-(pyridin-2-yl)-7-(trimethylsilyl)isoindolin-1-one (247r)



Prepared from amide **245a**, 2-ethynylpyridine and RuCp*Cl(cod) (20 mg, 20 mol%) over 24 h according to General Cyclization Procedure B (crude ratio **247r**:**248a** = 2:1) and purified by flash column chromatography (3:1 petrol 40–60 °C: Et_2O) to give the *isoindolinone* **247r** as a colorless oil (49 mg, 0.13 mmol, 50%); R_f = 0.40 (1:1 petrol 40–60 °C: Et_2O); ν_{max} (film/cm^{-1}) 2973s (C-H), 1686s (C=O), 1587s, 1409s; ^{1}H NMR (600 MHz; DMSO-d_6) 8.71–8.70 (1H, m, Ar*H*), 8.26–8.25 (1H, m, Ar*H*), 8.20–8.20 (1H, m, Ar*H*), 7.99–7.98 (1H, m, Ar*H*), 7.93–7.89 (1H, m, Ar*H*), 7.40–7.35 (3H, m, Ar*H*), 7.31–7.27 (3H, m, Ar*H*), 4.75 (2H, s, CH_2N), 4.42 (2H, s, CH_2N), 0.42 (9H, s, Si(CH_3)$_3$); ^{13}C NMR (150 MHz; DMSO-d_6) 168.2 (*C*(O)), 155.7 (*Ar*), 149.8 (*Ar*), 142.5 (*Ar*), 140.3 (*Ar*), 137.6 (*Ar*), 137.5 (*Ar*), 137.5 (*Ar*), 137.1 (*Ar*), 132.3 (*Ar*), 128.8 (*Ar*), 127.7 (*Ar*), 127.4 (*Ar*), 123.1 (*Ar*), 122.5 (*Ar*), 121.0 (*Ar*), 49.3 (*C*H_2N), 45.6 (*C*H_2N), –0.3 (Si(*C*H_3)$_3$). HRMS (CI$^+$) found [M+H]$^+$ 371.1708; $C_{23}H_{25}N_2OSi$ requires 373.1731.

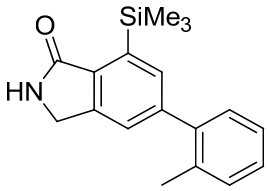
5-Butyl-7-(trimethylsilyl)isoindolin-1-one (264a)



Prepared from amide **245b**, 1-hexyne and Cp*RuCl(cod) (10 mg, 10 mol%) over 24 h according to the General Cyclization Procedure B (crude ratio **264a**:**265** = 2:1) and purified by flash column chromatography (5:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **264a** as a white crystalline solid (35 mg, 0.13 mmol, 51%); m.p. 140–142 °C; R_f = 0.57 (2:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3307m (N-H), 2968s (C-H), 1690s (C=O); ^{1}H NMR (600 MHz; DMSO-d_6) 8.37 (1H, s, N*H*), 7.36 (1H, s, Ar*H*), 7.33 (1H, s, Ar*H*), 4.30 (2H, s, CH_2N), 2.66 (2H, t, *J* = 7.7, ArCH_2CH$_2$), 1.59–1.53 (2H, m, ArCH$_2$CH_2), 1.32 (2H, sextet, *J* = 7.4, CH_2CH$_3$), 0.90 (3H, t, *J* = 7.4, CH$_2$CH_3), 0.32 (9H, s, Si(CH_3)$_3$); ^{13}C NMR (150 MHz; DMSO-d_6) 171.2 (*C*(O)), 144.7 (*Ar*), 144.6 (*Ar*), 136.6 (*Ar*), 134.9 (*Ar*), 133.9 (*Ar*), 124.1 (*Ar*), 44.7 (*C*H_2N), 35.1 (Ar*C*H$_2$CH$_2$), 33.3

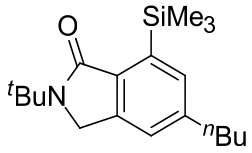
(ArCH$_2$*C*H$_2$), 21.9 (*C*H$_2$CH$_3$), 13.8 (CH$_2$*C*H$_3$), –0.3 (Si(*C*H$_3$)$_3$); HRMS (ES$^+$) found [M-Me]$^+$ 246.1302; $C_{14}H_{20}NOSi$ requires 246.1314.

5-(*o*-Tolyl)-7-(trimethylsilyl)isoindolin-1-one (264b)



Prepared from amide **245b**, 2-ethynyltoluene and RuCp*Cl(cod) (10 mg, 10 mol%) over 24 h according to the General Cyclization Procedure B (crude ratio **264b**:**265** = 7:1) and purified by flash column chromatography (2:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **264b** as a white crystalline solid (48 mg, 0.16 mmol, 62%); m.p. 133–135 °C; R_f = 0.30 (2:1 EtOAc: petrol 40–60 °C); ν_{max} (film/cm^{-1}) 3190 (N-H), 2947s (C-H), 1690s (C=O), 1450s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 8.53 (1H, s, N*H*), 7.53 (1H, s, Ar*H*), 7.43 (1H, s, Ar*H*), 7.33–7.24 (4H, m, Ar*H*), 4.40 (2H, s, C*H*$_2$N), 2.24 (3H, s, ArC*H*$_3$), 0.32 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 171.0 (*C*(O)), 144.4 (*Ar*), 143.0 (*Ar*), 141.0 (*Ar*), 136.7 (*Ar*), 135.9 (*Ar*), 134.7 (*Ar*), 134.4 (*Ar*), 130.5 (*Ar*), 129.6 (*Ar*), 127.7 (*Ar*), 126.1 (*Ar*), 125.0 (*Ar*), 45.0 (*C*H$_2$N), 20.2 (Ar*C*H$_3$), –0.3 (Si*C*H$_3$)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 296.1458; $C_{18}H_{22}NOSi$ requires 296.1470.

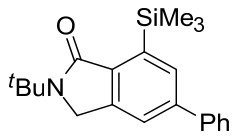
2-(*tert*-Butyl)-5-butyl-7-(trimethylsilyl)isoindolin-1-one (267a)



Prepared from amide **245c,** 1-hexyne and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to General Cyclization Procedure B (crude ratio **267a**:**268** = 10:1) and purified by flash column chromatography (30:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **267a** (70 mg, 0.22 mmol, 84%); R_f = 0.36 (30:1 EtOAc:petrol 40–60 °C); ν_{max} (film/cm^{-1}) 2957s (C-H), 1681s (C=O), 1455s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.32 (1H, s, Ar*H*), 7.31 (1H, s, Ar*H*), 4.48 (2H, s, C*H*$_2$N), 2.65 (2H, t, *J* = 7.7 ArC*H*$_2$CH$_2$), 1.54 (2H, m, ArCH$_2$C*H*$_2$), 1.47 (9H, s, C(C*H*$_3$)$_3$), 1.30 (2H, sextet, *J* = 7.3, C*H*$_2$CH$_3$), 0.89 (3H, t, *J* = 7.3, CH$_2$C*H*$_3$), 0.31 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.9 (*C*(O)), 144.3 (*Ar*), 141.7 (*Ar*), 136.3 (*Ar*), 136.0 (*Ar*), 134.0 (*Ar*), 123.4 (*Ar*), 53.5 (*C*Me$_3$), 47.8

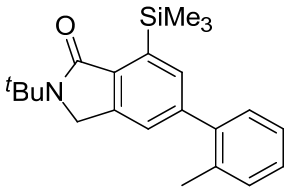
(*C*H$_2$N), 35.1 (Ar*C*H$_2$CH$_2$), 33.4 (ArCH$_2$*C*H$_2$), 27.5 (C(*C*H$_3$)$_3$), 21.8 (*C*H$_2$CH$_3$), 13.8 (CH$_2$*C*H$_3$), –0.2 (Si(CH$_3$)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 318.2252; C$_{19}$H$_{32}$NOSi requires 318.2248.

2-(*tert*-Butyl)-5-phenyl-7-(trimethylsilyl)isoindolin-1-one (267b)



Prepared from amide **245c**, phenylacetylene and RuCp*Cl(cod) (4 mg, 4 mol%) over 24 h according to General Cyclization Procedure B (crude ratio **267b**:**268** > 10:1) and purified by flash column chromatography (35:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **267b** as a white crystalline solid (79 mg, 0.23 mmol, 89%); m.p. 73–75 °C; R$_f$ = 0.36 (30:1 EtOAc: petrol 40–60 °C); ν_{max} (film/cm^{-1}) 2963s (C-H), 1677s (C=O), 1448s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.78 (1H, s, Ar*H*), 7.72–7.70 (1H, m, Ar*H*), 7.69–7.67 (2H, m, Ar*H*), 7.50 (2H, t, *J* = 9.3, Ar*H*), 7.43–7.39 (1H, m, Ar*H*), 4.60 (2H, s, C*H*$_2$N), 1.51 (9H, s, C(C*H*$_3$)$_3$), 0.37 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.6 (*C*(O)), 142.2 (*Ar*), 141.8 (*Ar*), 140.2 (*Ar*), 137.7 (*Ar*), 137.0 (*Ar*), 132.4 (*Ar*), 129.1 (*Ar*), 127.9 (*Ar*), 127.2 (*Ar*), 122.2 (*Ar*), 53.7 (*C*Me$_3$), 48.1 (*C*H$_2$N), 27.5 (*C*(*C*H$_3$)$_3$), –0.3 (Si(*C*H$_3$)$_3$); HRMS (ES$^+$) found [M+H]$^+$ 338.1940; C$_{21}$H$_{28}$NOSi requires 338.1940.

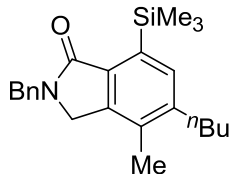
2-(*tert*-Butyl)-5-(*o*-tolyl)-7-(trimethylsilyl)isoindolin-1-one (267c)



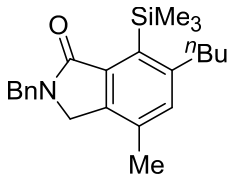
Prepared from amide **245c**, 2-ethynyltoluene and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to the General Cyclization Procedure B (crude ratio **267c**:**268** >10:1) and purified by flash column chromatography (20:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **267c** as a yellow oil (87 mg, 0.25 mmol, 94%); R$_f$ = 0.31 (20:1 EtOAc: petrol 40–60 °C); ν_{max} (film/cm^{-1}) 2973s (C-H), 1680s (C=O), 1452s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.48 (1H, s, Ar*H*), 7.40 (1H, s, Ar*H*), 7.31–7.21 (3H, m, Ar*H*), 7.21–7.18 (1H, m, Ar*H*), 4.58 (2H, s, C*H*$_2$N), 2.21 (3H, s, ArC*H*$_3$), 1.49 (9H, s, C(C*H*$_3$)$_3$), 0.33 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.6 (*C*(O)), 142.9 (*Ar*), 141.5 (*Ar*), 141.1 (*Ar*), 137.3 (*Ar*), 136.1 (*Ar*), 134.7 (*Ar*), 134.4 (*Ar*), 130.5 (*Ar*), 129.6 (*Ar*),

127.6 (*Ar*), 126.0 (*Ar*), 124.3 (*Ar*), 53.6 (*C*Me$_3$), 48.0 (*C*H$_2$N), 27.4 (C(*C*H$_3$)$_3$), 20.2 (Ar*C*H$_3$), –0.3 (Si(*C*H$_3$)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 352.2088; $C_{22}H_{30}NOSi$ requires 352.2097.

2-Benzyl-5-butyl-4-methyl-7-(trimethylsilyl)isoindolin-1-one (273a) and 2-Benzyl-6-butyl-4-methyl-7-(trimethylsilyl)isoindolin-1-one (274a)



273a



274a

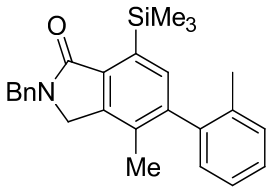
Prepared from amide **245e** and 1-hexyne according to the General Cyclization Procedure C (crude ratio **273a**:**274a** = 9:1) and purified by flash column chromatography (15:1 petrol 40–60 °C:EtOAc) to give a mixture of the *isoindolinone* **273a** and the *isoindolinone* **274a** as a colorless oil (10 mg, 0.027 mmol, 11%; **273a**:**274a** = 3:1). Further elution of the column gave more of the *isoindolinone* **273a** as a colorless oil (55 mg, 0.15 mmol, 58%).

***Isoindolinone* 273a:** R_f = 0.75 (9:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2956s (C-H), 1688s (C=O), 1454s, 1409s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.37–7.34 (2H, m, Ar*H*), 7.31 (1H, s, Ar*H*), 7.29–7.26 (3H, m, Ar*H*), 4.71 (2H, s, NC*H*$_2$), 4.27 (2H, s, NC*H*$_2$), 2.65 (2H, t, *J* = 7.8, ArC*H*$_2$CH$_2$), 2.17 (3H, s, ArC*H*$_3$), 1.50–1.45 (2H, m, ArCH$_2$C*H*$_2$), 1.35 (2H, sextet, *J* =7.3, C*H*$_2$CH$_3$), 0.91 (3H, t, *J* = 7.3, CH$_2$C*H*$_3$), 0.34 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 169.0 (*C*(O)), 143.0 (*Ar*), 141.6 (*Ar*), 137.8 (*Ar*), 135.0 (*Ar*), 134.2 (*Ar*), 133.6 (*Ar*), 131.6 (*Ar*), 128.7 (*Ar*), 127.7 (*Ar*), 123.3 (*Ar*), 48.6 (*C*H$_2$N), 45.5 (*C*H$_2$N), 32.5 (ArCH$_2$*C*H$_2$), 32.4 (Ar*C*H$_2$CH$_2$), 22.1 (*C*H$_2$CH$_3$), 13.8 (*C*H$_3$), 13.7 (*C*H$_3$), –0.3 (Si(*C*H$_3$)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 366.2246; $C_{23}H_{32}NOSi$ requires 366.2248. A NOESY experiment showed an NOE between; 2.65 (ArC*H*$_2$CH$_2$) and 2.17 (ArC*H*$_3$); 7.31 (Ar*H*) and 2.65 (ArC*H*$_2$CH$_2$); 7.31 (Ar*H*) and 0.34 (Si(C*H*$_3$)$_3$).

***Isoindolinone* 274a**: R_f = 0.77 (9:1 petrol 40–60 °C:EtOAc); ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.37–7.34 (2H, m, Ar*H*), 7.30–7.26 (3H, m, Ar*H*), 7.13 (1H, s, Ar*H*), 4.70 (2H, s, NC*H*$_2$), 4.22 (2H, s, NC*H*$_2$), 2.73 (2H, t, *J* = 7.7, ArC*H*$_2$CH$_2$), 2.20 (3H, s, ArC*H*$_3$), 1.44–1.40 (2H, m, ArCH$_2$C*H*$_2$), 1.32 (2H, sextet, *J* =7.4, C*H*$_2$CH$_3$), 0.89 (3H, t, *J* = 7.4, CH$_2$C*H*$_3$), 0.40 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.9 (*C*(O)), 149.1

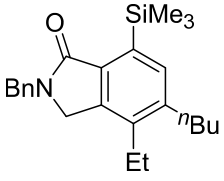
(*Ar*), 139.1 (*Ar*), 137.4 (*Ar*), 133.7 (*Ar*), 133.3 (*Ar*), 132.4 (*Ar*), 128.5 (*Ar*), 127.7 (*Ar*), 47.7 (*C*H_2N), 45.6 (*C*H_2N), 36.4 (ArCH$_2$*C*H$_2$), 35.7 (Ar*C*H$_2$CH$_2$), 22.1 (*C*H_2CH$_3$), 16.9 (Ar*C*H$_3$), 14.0 (CH$_2$*C*H$_3$), 3.4 (Si(*C*H$_3$)$_3$). Two aromatic ^{13}C resonances were obscured by compound **273a**.

2-Benzyl-4-methyl-5-(*o*-tolyl)-7-(trimethylsilyl)isoindolin-1-one (273b)

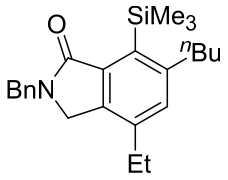


Prepared from amide **245e** and 2-ethynyltoluene according to the General Cyclization Procedure C to give the *isoindolinone* **273b** as a yellow oil (114 mg, approximately 90% pure by ^{1}H NMR, 0.23 mmol, 88%); R_f = 0.22 (18:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3950s (C-H), 1688s (C=O), 1410s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.37–7.21 (9H, m, Ar*H*), 7.06 (1H, d, *J* = 7.2, Ar*H*), 4.78 (1H, d, *J* = 15.4, C*H*$_2$N), 4.74 (1H, d, *J* = 15.4, C*H*$_2$N), 4.39 (1H, d, *J* = 17.4, C*H*H'N), 4.34 (1H, d, *J* = 17.4, CH*H*'N), 1.98 (3H, s, ArC*H*$_3$), 1.92 (3H, s, ArC*H*$_3$), 0.34 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.8 (*C*(O)), 143.1 (*Ar*), 141.6 (*Ar*), 140.1 (*Ar*), 137.3 (*Ar*), 135.4 (*Ar*), 135.2 (*Ar*), 134.9 (*Ar*), 133.8 (*Ar*), 131.6 (*Ar*), 130.0 (*Ar*), 129.1 (*Ar*), 128.7 (*Ar*), 127.8 (*Ar*), 127.6 (*Ar*), 127.1 (*Ar*), 125.8 (*Ar*), 48.7 (*C*H$_2$N), 45.6 (*C*H$_2$N), 19.6 (Ar*C*H$_3$), 14.7(Ar*C*H$_3$), –0.3 (Si(*C*H$_3$)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 400.2106; $C_{26}H_{30}NOSi$ requires 400.2091. This compound was unstable to flash column chromatography.

2-Benzyl-5-butyl-4-ethyl-7-(trimethylsilyl)isoindolin-1-one (273c) and 2-Benzyl-6-butyl-4-ethyl-7-(trimethylsilyl)isoindolin-1-one (274c)



273c



274c

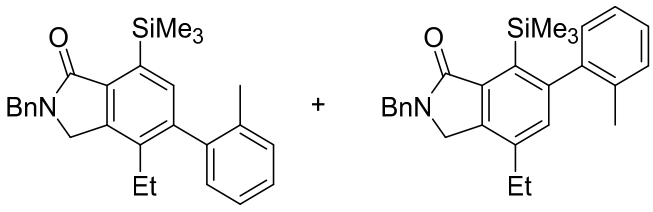
Prepared from amide **245f** and 1-hexyne according to the General Cyclization Procedure C (crude ratio **273c**:**274c** = 2:1) and purified by flash column chromatography (18:1 petrol 40–60 °C:EtOAc) to give a mixture of the *isoindolinone* **273c** and the *isoindolinone* **274c** as a colorless oil (40 mg, 0.11 mmol, 40%, **273c**:**274c** = 2:3). Further elution of the

column gave more of the *isoindolinone* **273c** as a colorless oil (17 mg, 0.045 mmol, 17%); ν_{max} (film/cm^{-1}) 2957s (C-H), 1690s (C=O), 1409s; HRMS (CI$^+$) found [M+H]$^+$ 380.2410; $C_{24}H_{34}NOSi$ requires 380.2404.

***Isoindolinone* 273c:** R_f = 0.25 (18:1 petrol 40–60 °C:EtOAc); ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.36–7.33 (3H, m, Ar*H*), 7.29–7.26 (3H, m, Ar*H*), 4.71 (2H, s, C*H*$_2$N), 4.33 (2H, s, C*H*$_2$N), 2.65 (2H, t, *J* = 7.9, ArC*H*$_2$CH$_2$), 2.58 (2H, q, *J* = 7.6, ArC*H*$_2$CH$_3$), 1.52–1.47 (2H, m, ArCH$_2$C*H*$_2$), 1.37 (2H, sextet, *J* = 7.4, CH$_2$C*H*$_2$CH$_3$), 1.06 (3H, t, *J* = 7.6, ArCH$_2$C*H*$_3$), 0.91 (3H, t, *J* = 7.4, CH$_2$CH$_2$C*H*$_3$), 0.34 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 169.0 (*C*(O)), 142.4 (*Ar*), 140.9 (*Ar*), 137.8 (*Ar*), 137.4 (*Ar*), 135.5 (*Ar*), 134.4 (*Ar*), 133.9 (*Ar*), 128.7 (*Ar*), 127.7 (*Ar*), 127.3 (*Ar*), 48.2 (*C*H$_2$N), 45.5 (*C*H$_2$N), 33.6 (ArCH$_2$*C*H$_2$), 31.5 (Ar*C*H$_2$CH$_2$), 22.2 (ArCH$_2$CH$_2$*C*H$_2$), 21.4 (Ar*C*H$_2$CH$_3$), 14.3 (ArCH$_2$*C*H$_3$), 13.9 (CH$_2$CH$_2$*C*H$_3$), –0.3 (Si(*C*H$_3$)$_3$).

***Isoindolinone* 274c:** R_f = 0.31 (18:1 petrol 40–60 °C:EtOAc); ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.36–7.32 (2H, m, Ar*H*), 7.29–7.25 (3H, m, Ar*H*), 7.14 (1H, s, Ar*H*), 4.69 (2H, s, C*H*$_2$N), 4.25 (2H, s, C*H*$_2$N), 2.74 (2H, t, *J* = 7.9, ArC*H*$_2$CH$_2$), 2.52 (2H, q, *J* = 7.6, ArC*H*$_2$CH$_3$), 1.45–1.40 (2H, m, ArCH$_2$C*H*$_2$), 1.31 (2H, sextet, *J* = 7.2, CH$_2$C*H*$_2$CH$_3$), 1.13 (3H, t, *J* = 7.6, ArCH$_2$C*H*$_3$), 0.87 (3H, t, *J* = 7.2, CH$_2$CH$_2$C*H*$_3$), 0.40 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 169.0 (*C*(O)), 149.3 (*Ar*), 139.0 (*Ar*), 138.3 (*Ar*), 137.5 (*Ar*), 135.5 (*Ar*), 132.6 (*Ar*), 131.9 (*Ar*), 127.7 (*Ar*), 47.4 (*C*H$_2$N), 45.6 (*C*H$_2$N), 36.5 (ArCH$_2$*C*H$_2$), 35.9 (Ar*C*H$_2$CH$_2$), 23.9 (Ar*C*H$_2$CH$_3$), 22.1 (ArCH$_2$CH$_2$*C*H$_2$), 14.0 (CH$_2$*C*H$_3$), 13.8 (CH$_2$*C*H$_3$), 0.3 (Si(*C*H$_3$)$_3$). Two aromatic ^{13}C resonances were obscured by compound **273c**.

2-Benzyl-4-ethyl-5-(*o*-tolyl)-7-(trimethylsilyl)isoindolin-1-one (273d) and 2-benzyl-4-Ethyl-6-(*o*-tolyl)-7-(trimethylsilyl)isoindolin-1-one (274d)

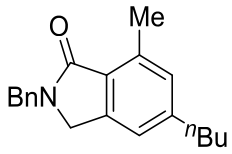


273d **274d**

Prepared from amide **245f** and 2-ethynyltoluene according to the General Cyclization Procedure C (crude ratio **273d**:**274d** = 5:1). This was purified by flash column

chromatography (18:1 petrol 40–60 °C:EtOAc) to give a mixture of the *isoindolinone* **273d** and the *isoindolinone* **274d** as a colorless oil (80 mg, 0.19 mmol, 73%; **273d**:**274d** = 5:1); R_f = 0.33 (18:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2964s (C-H), 1690s (C=O), 1410s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.39–7.23 (8H, m, Ar*H* **273d**; 8H, m, Ar*H* **274d**), 7.19 (1H, s, Ar*H* **273d**), 7.11 (1H, d, *J* = 7.6, Ar*H* **273d**), 7.04 (1H, s, Ar*H* **274d**), 7.00 (1H, d, *J* = 7.6, Ar*H* **274d**), 5.78–4.73 (2H, m, C*H*$_2$N **273d**; 2H, m, C*H*$_2$N, **274d**), 4.48–4.40 (2H, m, C*H*$_2$N **273d**; 2H, m, C*H*$_2$N, **274d**), 2.60 (2H, q, *J* = 7.8, C*H*$_2$CH$_3$ **274d**), 2.50–2.42 (1H, m, C*H*H'CH$_3$ **273d**), 2.27–2.19 (1H, m, CH*H*'CH$_3$ **273d**), 2.05 (3H, s, ArC*H*$_3$ **274d**), 1.98 (3H, s, ArC*H*$_3$ **273d**), 1.15 (3H, t, *J* = 7.6, CH$_2$C*H*$_3$ **274d**), 0.82 (3H, t, *J* = 7.7, CH$_2$C*H*$_3$ **273d**), 0.34 (9H, s, Si(C*H*$_3$)$_3$ **273d**), –0.06 (9H, s, Si(C*H*$_3$)$_3$ **274d**); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.8 (*C*(O)), 168.7 (*C*(O)), 148.4 (*Ar*), 144.0 (*Ar*), 142.6 (*Ar*), 141.0 (*Ar*), 140.0 (*Ar*), 139.4 (*Ar*), 138.8 (*Ar*), 137.8 (*Ar*), 137.7 (*Ar*), 137.4 (*Ar*), 135.9 (*Ar*), 135.4 (*Ar*), 135.2 (*Ar*), 135.1 (*Ar*), 134.1 (*Ar*), 133.1 (*Ar*), 131.5 (*Ar*), 130.0 (*Ar*), 129.7 (*Ar*), 129.2 (*Ar*), 128.7 (*Ar*), 127.8 (*Ar*), 127.7 (*Ar*), 127.7 (*Ar*), 127.5 (*Ar*), 127.4 (*Ar*), 125.6 (*Ar*), 125.3 (*Ar*), 48.4 (*C*H$_2$N), 47.7 (*C*H$_2$N), 45.7 (*C*H$_2$N), 45.6 (*C*H$_2$N), 23.8 (*C*H$_2$CH$_3$), 22.2 (*C*H$_2$CH$_3$), 20.2 (Ar*C*H$_3$), 19.9 (Ar*C*H$_3$), 13.6 (CH$_2$*C*H$_3$), 1.6 (Si(*C*H$_3$)$_3$), –0.3 (Si(*C*H$_3$)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 414.2245; $C_{27}H_{32}NOSi$ requires 414.2248.

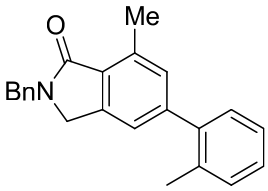
2-Benzyl-5-butyl-7-methylisoindolin-1-one (273a)[137]



Prepared from amide **245g**, 1-hexyne and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to the General Cyclization Procedure B and purified by flash column chromatography (7:1 petrol 40–60 °C:EtOAc) to give the isoindolinone **273a** as a colorless oil (65 mg, 0.22 mmol, 85%); R_f = 0.31 (7:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2927s (C-H), 1681s (C=O), 1615s, 1453s, 1407s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.36–7.32 (2H, m, Ar*H*), 7.28–7.24 (3H, m, Ar*H*), 7.13 (1H, s, Ar*H*), 7.04 (1H, s, Ar*H*), 4.67 (2H, s, C*H*$_2$N), 4.24 (2H, s, C*H*$_2$N), 2.61–2.57 (5H, m, ArC*H*$_3$; ArC*H*$_2$CH$_2$), 1.53 (2H, quintet, *J* = 7.5, ArCH$_2$C*H*$_2$), 1.28 (2H, sextet, *J* = 7.5, C*H*$_2$CH$_3$), 0.87 (3H, t, *J* = 7.5, CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.2 (*C*(O)), 145.9 (*Ar*), 142.6 (*Ar*), 137.7 (*Ar*), 136.0 (*Ar*), 129.9 (*Ar*), 128.7 (*Ar*), 127.7 (*Ar*), 127.3 (*Ar*), 126.8

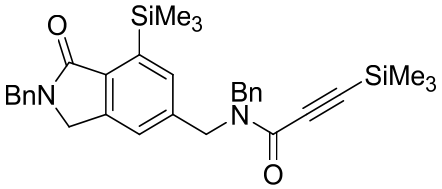
(*Ar*), 120.6 (*Ar*), 48.5 (*C*H$_2$N), 45.1 (*C*H$_2$N), 34.9 (ArCH$_2$CH$_2$), 33.1 (ArCH$_2$*C*H$_2$), 21.8 (*C*H$_2$CH$_3$), 16.7 (Ar*C*H$_3$), 13.8 (CH$_2$*C*H$_3$); data in accordance with the literature.[137]

2-Benzyl-7-methyl-5-(*o*-tolyl)isoindolin-1-one (273b)



Prepared from amide **245g**, 2-ethynyltoluene and RuCp*Cl(cod) (3 mg, 3 mol%) over 16 h according to the General Cyclization Procedure B to give the *isoindolinone* **273b** as a yellow oil (80 mg, 0.24 mmol, 94%); R$_f$ = 0.31 (5:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2923s (C-H), 1684s (C=O), 1614s 1495s, 1453s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.37–7.34 (2H, m, Ar*H*), 7.30–7.22 (7H, m, Ar*H*), 71.9–7.17 (2H, m, Ar*H*), 4.71 (2H, s, C*H*$_2$N), 4.31 (2H, s, C*H*$_2$N), 2.63 (3H, s, ArC*H*$_3$), 2.21 (3H, s, ArC*H*$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 168.0 (*C*(O)), 144.1 (*Ar*), 142.4 (*Ar*), 140.7 (*Ar*), 137.7 (*Ar*), 136.1 (*Ar*), 134.7 (*Ar*), 130.5 (*Ar*), 130.4 (*Ar*), 129.5 (*Ar*), 128.7 (*Ar*), 127.8 (*Ar*), 127.7 (*Ar*), 127.4 (*Ar*), 126.0 (*Ar*), 121.5 (*Ar*), 48.7 (*C*H$_2$N), 45.3 (*C*H$_2$N), 20.2 (Ar*C*H$_3$), 16.8 (Ar*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 328.1688; C$_{23}$H$_{22}$NO requires 328.1696.

***N*-Benzyl-*N*-((2-benzyl-1-oxo-7-(trimethylsilyl)isoindolin-5-yl)methyl)-3-(trimethylsilyl)propiolamide (248a)**

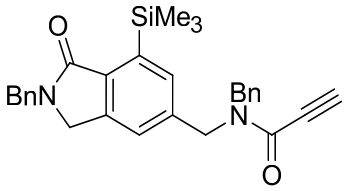


Isolated from the certain alkyne cyclotrimerization reaction involving amide **245a**.

The *isoindolinone* **248a** was isolated as a colorless oil; R$_f$ = 0.24 (6:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3279s (CC-H), 2960w (C-H), 2108w (C≡C), 1630s (C=O), 1415s; ^{1}H NMR (600 MHz; DMSO-d$_6$) a 1:1 mixture of rotamers; 7.46–7.17 (12H, m, Ar*H*; 12H, m, Ar*H*), 4.79 (2H, s, C*H*$_2$N), 4.73 (2H, s, C*H*$_2$N), 4.72 (2H, s, C*H*$_2$N), 4.71 (2H, s, C*H*$_2$N), 4.55 (2H, s, C*H*$_2$N), 4.47 (2H, s, C*H*$_2$N), 4.32 (2H, s, C*H*$_2$N), 4.30 (2H, s, C*H*$_2$N), 0.34 (9H, s, Si(C*H*$_3$)$_3$), 0.33 (9H, s, Si(C*H*$_3$)$_3$), 0.17 (9H, s, Si(C*H*$_3$)$_3$), 0.13 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (125 MHz; DMSO-d$_6$) a mixture of rotamers; 168.2 (*C*(O)), 168.2

(*C*(O)), 153.3 (*Ar*), 153.3 (*Ar*), 142.3 (*Ar*), 138.9 (*Ar*), 138.7 (*Ar*), 137.6 (*Ar*), 137.6 (*Ar*), 137.4 (*Ar*), 137.2 (*Ar*), 136.5 (*Ar*), 136.5 (*Ar*), 136.0 (*Ar*), 135.7 (*Ar*), 133.6 (*Ar*), 133.0 (*Ar*), 128.7 (*Ar*), 128.7 (*Ar*), 128.5 (*Ar*), 127.9 (*Ar*), 127.7 (*Ar*), 127.7 (*Ar*), 127.7 (*Ar*), 127.5 (*Ar*), 127.4 (*Ar*), 127.4 (*Ar*), 123.4 (*Ar*), 123.3 (*Ar*), 97.4 (*C*≡C), 97.4 (*C*≡C), 96.4 (*C*≡C), 51.9 (*C*H_2N), 51.9 (*C*H_2N), 49.0 (*C*H_2N), 47.3 (*C*H_2N), 47.3 (*C*H_2N), 45.4 (*C*H_2N), –0.4 (Si(*C*H_3)$_3$), –0.4 (Si(*C*H_3)$_3$), –1.0 (Si(*C*H_3)$_3$), –1.0 (Si(*C*H_3)$_3$); HRMS (EI$^+$) found [M+H]$^+$ 539.2548; $C_{32}H_{39}N_2O_2Si_2$ requires 539.2550.

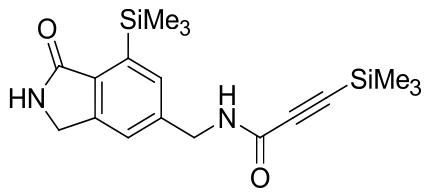
N-Benzyl-*N*-((2-benzyl-1-oxo-7-(trimethylsilyl)isoindolin-5-yl)methyl)propiolamide (248b)



Isolated from the specific alkyne cyclotrimerization reaction involving amide **248b**.

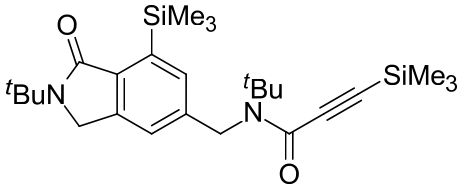
The *isoindolinone* **248b** was isolated as a colorless oil; R_f = 0.10 (6:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3288s (CC-H), 2932s (C-H), 2104w (C≡C), 1653s (C=O), 1601, 1453s; ^{1}H NMR (600 MHz; $CDCl_3$) a 1:1 mixture of rotamers; 7.44–7.14 (12 H, m, Ar*H*; 12H, m, Ar*H*), 4.80 (2H, s, CH_2N), 4.73 (2H, s, CH_2N), 4.71 (2H, s, CH_2N), 4.70 (2H, s, CH_2N), 4.64 (1H, s, H*C*≡C), 4.63 (1H, s, H*C*≡C), 4.53 (2H, s, CH_2N), 4.45 (2H, s, CH_2N), 4.32 (2H, s, CH_2N), 4.29 (2H, s, CH_2N), 0.34 (9H, s, Si(CH_3)$_3$), 0.32 (9H, s, Si(CH_3)$_3$); ^{13}C NMR (125 MHz; DMSO-d_6) a mixture of rotamers; 168.2 (*C*(O)), 168.1 (*C*(O)), 153.3 (*Ar*), 153.3 (*Ar*), 142.3 (*Ar*), 142.2 (*Ar*), 138.6 (*Ar*), 138.6 (*Ar*), 137.6 (*Ar*), 137.6 (*Ar*), 137.4 (*Ar*), 137.2 (*Ar*), 136.3 (*Ar*), 136.2 (*Ar*), 136.0 (*Ar*), 135.7 (*Ar*), 133.5 (*Ar*), 133.0 (*Ar*), 133.1 (*Ar*), 128.7 (*Ar*), 128.4 (*Ar*), 127.8 (*Ar*), 127.7 (*Ar*), 127.6 (*Ar*), 127.4 (*Ar*), 127.4 (*Ar*), 123.4 (*Ar*), 123.1 (*Ar*), 82.9 (*C*≡C), 75.9 (*C*≡C), 51.6 (*C*H_2N), 51.6 (*C*H_2N), 49.0 (*C*H_2N), 49.0 (*C*H_2N), 47.1 (*C*H_2N), 47.0 (*C*H_2N), 45.4 (*C*H_2N), –0.5 (Si(*C*H_3)$_3$).

_N_-((1-Oxo-7-trimethylsiyl)isoindolin-5-yl)methyl)-3-(trimethylsilyl)propiolamide (265)



A solution of RuCp*Cl(cod) (10 mg, 0.026 mmol, 10 mol%) in CPME (1.1 mL) was added dropwise to a stirring solution of amide **245b** (47 mg, 0.26 mmol) in CPME (1.6 mL) at RT. The reaction was stirred for 16 h before the reaction mixture was filtered through a silica pad, eluting with EtOAc. The filtrate was concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (2:1 EtOAc:petrol 40–60 °C) to give the *isoindolinone* **265** as a white crystalline solid (47 mg, 0.10 mmol, 79%); m.p. 104–106 °C; R_f = 0.36 (2:1 EtOAc:petrol 40–60 °C); ν_{max} (film/cm^{-1}) 3321m (N-H), 3208m (N-H), 2957m (C-H), 1674s (C=O), 1655s (C=O), 1601m; ^{1}H NMR (600 MHz; DMSO-d$_6$) 9.30 (1H, t, *J* = 5.7, N*H* straight chain amide), 8.46 (1H, s, N*H* lactam), 7.42 (1H, s, Ar*H*), 7.40 (1H, s, Ar*H*), 4.38–4.31 (4H, m, C*H*$_2$N, C*H*$_2$N), 0.32 (9H, s, Si(C*H*$_3$)$_3$), 0.30 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 171.0 (*C*(O) lactam), 151.8 (*C*(O) straight chain amide), 144.6 (*Ar*), 140.7 (*Ar*), 136.9 (*Ar*), 136.1 (*Ar*), 133.1 (*Ar*), 123.3 (*Ar*), 98.8 (*C*≡C), 90.1 (*C*≡C), 44.8 (*C*H$_2$N), 42.5 (*C*H$_2$N), –0.4 (Si(*C*H$_3$)$_3$), –0.7 (Si(*C*H$_3$)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 359.1617; $C_{18}H_{27}N_2O_2Si_2$ requires 359.1611.

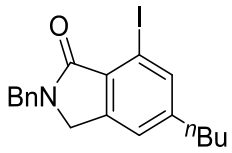
_N_-(*tert*-Butyl)-_N_-((2-(*tert*-butyl)-1-oxo-7-(trimethylsilyl)isoindolin-5-yl)methyl)-3-(trimethylsilyl)propiolamide (268)



RuCp*Cl(cod) (8 mg, 0.011 mmol, 10 mol%) was added dropwise to a stirring solution of amide **245c** (50 mg, 0.11 mmol) in CPME (2.2 mL) at RT. The reaction was stirred for 16 h before the reaction mixture was filtered through a silica pad, eluting with EtOAc. The filtrate was concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (10:1 EtOAc:petrol 40–60 °C) to give the *isoindolinone*

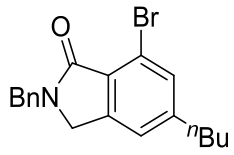
268 as a colorless oil (50 mg, 0.11 mmol, 100%); ν_{max} (film/cm^{-1}) 2963s (C-H), 1680s (C=O), 1631s (C=O); ^{1}H NMR (400 MHz; DMSO-d$_6$) 7.47 (1H, s, Ar*H*) 7.41 (1H, s, Ar*H*), 5.00 (2H, s, C*H*$_2$N), 4.54 (2H, s, C*H*$_2$N), 1.47 (9H, s, C(C*H*$_3$)$_3$), 1.31 (9H, s, C(C*H*$_3$)$_3$), 0.31 (9H, s, Si(C*H*$_3$)$_3$), 0.00 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (125 MHz; DMSO-d$_6$) 168.5 (*C*(O) lactam), 154.4 (*C*(O) straight chain amide), 141.8 (*Ar*), 141.1 (*Ar*), 137.5 (*Ar*), 136.2 (*Ar*), 131.6 (*Ar*), 121.4 (*Ar*), 98.6 (*C*≡C), 93.6 (*C*≡C), 57.7 (*C*Me$_3$), 53.6 (*C*Me$_3$), 50.4 (*C*H$_2$N), 47.9 (*C*H$_2$N), –0.4 (Si(*C*H$_3$)$_3$), –1.1 (Si(*C*H$_3$)$_3$); HRMS (CI$^+$) found [M]$^+$ 470.2791; $C_{26}H_{42}N_2O_2Si_2$ requires 470.2779.

2-Benzyl-5-butyl-7-iodoisoindolin-1-one (275)



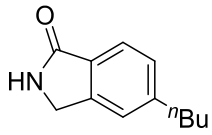
According to the modified procedure of Clayden *et al.*[149]: A solution of ICl (93 mg, 0.57 mmol) in CH_2Cl_2 (0.57 mL) was added dropwise to a stirring solution of isoindolinone **247a** (26 mg, 0.074 mmol) in CH_2Cl_2 (17 mL) at RT. The reaction was stirred for 3.5 h and aq. sat. $Na_2S_2O_3$ was added to afford a colorless solution. The reaction was extracted with CH_2Cl_2 (2 × 20 mL), dried ($MgSO_4$), and concentrated *in vacuo.* The crude product was purified by flash column chromatography (5:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **275** as a colorless oil (27 mg, 0.067 mmol, 90%); R_f = 0.20 (6:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2929s (C-H), 1690s (C=O), 1609s, 1453s, 1408s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.74 (1H, s, Ar*H*), 7.38 (1H, s, Ar*H*), 7.36–7.33 (2H, m, Ar*H*), 7.29–7.25 (3H, m, Ar*H*), 4.69 (2H, s, C*H*$_2$N), 4.23 (2H, s, C*H*$_2$N), 2.60 (2H, t, *J* = 7.7, ArC*H*$_2$CH$_2$), 1.53 (2H, m, ArCH$_2$C*H*$_2$), 1.27 (2H, sextet, *J* = 7.4, C*H*$_2$CH$_3$), 0.87 (3H, t, *J* = 7.4, C*H*$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 165.9 (*C*(O)), 148.1 (*Ar*), 144.6 (*Ar*), 139.0 (*Ar*), 137.4 (*Ar*), 129.4 (*Ar*), 128.7 (*Ar*), 127.7 (*Ar*), 127.4 (*Ar*), 123.4 (*Ar*), 89.9 (*C*I), 47.7 (*C*H$_2$N), 45.6 (*C*H$_2$N), 34.2 (Ar*C*H$_2$CH$_2$), 32.9 (ArCH$_2$*C*H$_2$), 21.7 (*C*H$_2$CH$_3$), 13.8 (*C*H$_3$); HRMS (ES$^+$) found [M+H]$^+$ 406.0663; $C_{19}H_{21}INO$ requires 406.0668.

2-Benzyl-7-bromo-5-butylisoindolin-1-one (276)



According to the modified procedure of Snieckus *et al.*[150]: A solution of Br_2 (118 mg, 0.738 mmol) in CH_2Cl_2 (0.36 mL) was added dropwise to a stirring solution of the isoindolinone **247a** (26 mg, 0.074 mmol) in CH_2Cl_2 (0.36 mL) at RT. The reaction was stirred for 16 h and aq. sat. $Na_2S_2O_3$ was added to afford a colorless solution. The reaction was extracted with CH_2Cl_2 (2 × 20 mL), dried ($MgSO_4$), and concentrated *in vacuo.* The crude product was purified by flash column chromatography (10:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **276** as a colorless oil (21 mg, 0.058 mmol, 78%); R_f = 0.50 (5:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2928s (C-H), 1692s (C=O), 1615s, 1453s, 1408s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.49 (1H, s, Ar*H*), 7.37–7.33 (3H, m, Ar*H*), 7.29–7.26 (3H, m, Ar*H*), 4.69 (2H, s, C*H*$_2$N), 4.28 (2H, s, C*H*$_2$N), 2.64 (2H, t, *J* = 7.7, ArC*H*$_2$CH$_2$), 1.54 (2H, m, ArCH$_2$C*H*$_2$), 1.28 (2H, sextet, *J* = 7.4, C*H*$_2$CH$_3$), 0.87 (3H, t, *J* = 7.4, C*H*$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 165.3 (*C*(O)), 148.3 (*Ar*), 145.0 (*Ar*), 137.4 (*Ar*), 132.4 (*Ar*), 128.7 (*Ar*), 127.7 (*Ar*), 127.4 (*Ar*), 126.9 (*Ar*), 122.9 (*Ar*), 117.2 (*Ar*), 48.1 (*C*H$_2$N), 45.4 (*C*H$_2$N), 34.4 (Ar*C*H$_2$CH$_2$), 32.9 (ArCH$_2$*C*H$_2$), 21.7 (*C*H$_2$CH$_3$), 13.8 (*C*H$_3$); HRMS (ESI$^+$) found [M+H]$^+$ 358.0807; $C_{19}H_{21}{}^{79}BrNO$ requires 358.0807.

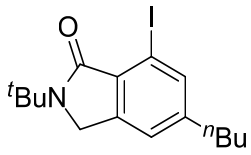
5-Butylisoindolin-1-one (277)



According to the modified procedure of Miranda *et al.*[151]: TfOH (0.50 mL) was added to the isoindolinone **267a**. (50 mg, 0.16 mmol). The resulting solution was stirred at RT for 30 minutes before being partitioned between EtOAc (20 mL) and water (20 mL). The aq. extract was washed with EtOAc (2 × 20 mL) and the combined organic extracts were washed with aq. sat. Na_2CO_3 (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. This was purified by flash column chromatography (3:1 EtOAc:petrol 40–60 °C) to give the *isoindolinone* **277** as a white crystalline solid (26 mg, 0.014 mmol, 88%); m.p. 145–147 °C; R_f = 0.57 (2:1 petrol 40–60 °C:EtOAc);

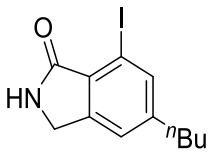
ν_{max} (film/cm^{-1}); 3203s (N-H), 3083s (C-H), 2932s (C-H), 1673s (C-H), 1451s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 8.50 (1H, s, N*H*), 7.56 (1H, d, *J* = 7.7, Ar*H*), 7.37 (1H, d, *J* = 7.7, Ar*H*), 4.32 (2H, s, C*H*$_2$N), 2.67 (2H, t, *J* = 7.7, ArC*H*$_2$CH$_2$), 1.59–1.54 (2H, m, ArCH$_2$C*H*$_2$), 1.30 (2H, sextet, *J* = 7.4, C*H*$_2$CH$_3$), 0.89 (3H, t, *J* = 7.4, C*H*$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 170.0 (*C*(O)), 146.2 (*Ar*), 144.5, (*Ar*), 130.4 (*Ar*), 128.0 (*Ar*), 123.4 (*Ar*), 122.6 (*Ar*), 44.8 (*C*H$_2$N), 39.1 (Ar*C*H$_2$CH$_2$), 35.0 (ArCH$_2$*C*H$_2$), 21.8 (*C*H$_2$CH$_3$), 13.8 (CH$_2$CH$_3$); HRMS (EI$^+$) found [M]$^+$ 189.1153; C$_{12}$H$_{15}$NO requires 189.1148.

2-(*tert*-Butyl)-5-butyl-7-iodoisoindolin-1-one



According to the modified procedure of Clayden *et al.*[149]: A solution of ICl (400 mg, 2.49 mmol) in CH$_2$Cl$_2$ (5.0 mL) was added dropwise to a stirring solution of isoindolinone **267a** (158 mg, 0.498 mmol) in CH$_2$Cl$_2$ (5.0 mL) at RT. The reaction was stirred for 2 h and the reaction mixture was diluted with sat. aq. NaHCO$_3$, before sat. aq. Na$_2$S$_2$O$_3$ was added dropwise to afford a colorless solution. The reaction was extracted with CH$_2$Cl$_2$ (2 × 20 mL), dried (MgSO$_4$), and concentrated *in vacuo* to give the *isoindolinone* as a yellow oil (183 mg, 0.492 mmol, 99%); R$_f$ = 0.31 (6:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2957s (C-H), 2928s (C-H), 1678s (C=O), 1607s, 1455s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.67 (1H, s, Ar*H*), 7.33 (1H, s, Ar*H*), 4.39 (2H, s, C*H*$_2$N), 2.57 (2H, t, *J* = 7.6, ArC*H*$_2$CH$_2$), 1.52–1.47 (2H, m, ArCH$_2$C*H*$_2$), 1.44 (9H, s, C(C*H*$_3$)$_3$), 1.25 (2H, sextet, *J* = 7.4, C*H*$_2$CH$_3$), 0.85 (3H, t, *J* = 7.4, CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 165.8 (*C*(O)), 147.4 (*Ar*), 144.1 (*Ar*), 138.8 (*Ar*), 130.5 (*Ar*), 122.9 (*Ar*), 89.0 (*C*I), 53.8 (*C*Me$_3$), 46.3 (*C*H$_2$N), 34.3 (Ar*C*H$_2$CH$_2$), 33.0 (ArCH$_2$*C*H$_2$), 27.4 (C(*C*H$_3$)$_3$), 21.7 (*C*H$_2$CH$_3$), 13.8 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 372.0837; C$_{19}$H$_{23}$INO requires 372.0824.

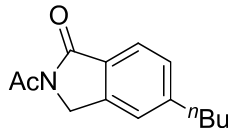
5-Butyl-7-iodoisoindolin-1-one (278)



TfOH (0.75 mL) was added to 2-(*tert*-butyl)-5-butyl-7-iodoisoindolin-1-one (156 mg, 0.420 mmol). The resulting solution was stirred at RT for 2 days before being partitioned

between EtOAc (20 mL) and water (20 mL). The aq. extract was washed with EtOAc (2 × 20 mL) and the combined organic extracts were washed with aq. sat. Na_2CO_3 (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. This was purified by flash column chromatography (1:1 EtOAc:petrol 40–60 °C) to give the *isoindolinone* **278** as a white crystalline solid (112 mg, 0.355, 85%); m.p. 137–139 °C; R_f = 0.37 (2:1 EtOAc:petrol 40–60 °C); ν_{max} (film/cm^{-1}) 3171s (N-H), 3073s (C-H) 2928s (C-H) 1702s (C=O), 1607s, 1457s; ^{1}H NMR (600 MHz; DMSO-d_6); 8.64 (1H, s, N*H*), 7.73 (1H, s, Ar*H*), 7.41 (1H, s, Ar*H*), 4.23 (2H, s, CH_2N), 2.63 (2H, t, *J* = 7.7, ArCH_2CH$_2$), 1.59–1.53 (2H, m, ArCH$_2$CH_2), 1.29 (2H, sextet, *J* = 7.4, CH_2CH$_3$), 0.88 (3H, t, *J* = 7.4, CH_3); ^{13}C NMR (150 MHz; DMSO-d_6); 168.5 (*C*(O)), 147.9 (*Ar*), 146.8 (*Ar*), 138.8 (*Ar*), 129.7 (*Ar*), 123.6 (*Ar*), 89.7 (*C*I), 43.0 (*C*H$_2$N), 34.2 (Ar*C*H$_2$CH$_2$), 33.0 (ArCH$_2$*C*H$_2$), 21.7 (CH_2CH$_3$), 13.8 (CH_3); HRMS (ES$^+$) found [M]$^+$ 315.0108; $C_{12}H_{14}INO$ requires 315.0120.

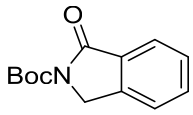
2-Acetyl-5-butylisoindolin-1-one (282)



According to the modified procedure of Clift and Silverman[154]: aq. HCl (8.0 mL, 12 M) was added to isoindolinone **277** (37 mg, 0.20 mmol). The reaction mixture was heated at reflux for 3 days before it was allowed to cool to RT. The reaction mixture was concentrated *in vacuo* and then it was dissolved in CH_2Cl_2 (5.0 mL). The resulting solution was stirred at RT and treated with NEt_3 (0.14 mL, 100 mg, 1.0 mmol) and Ac_2O (95 µl, 100 mg, 1.0 mmol). The reaction was stirred at RT for 16 h, quenched with water (1.0 mL) and filtered through a silica plug, eluting with EtOAc. The filtrate was concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (10:1 EtOAc:petrol 40–60 °C) to give the *isoindolinone* **282** as a white crystalline solid (26 mg, 0.11 mmol, 56%); m.p. = 69–71 °C; R_f = 0.29 (10:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2930s (C-H), 1712s (C=O ester), 1693s (C=O lactam), 1589s, 1439s; ^{1}H NMR (600 MHz; DMSO-d_6); 7.73 (1H, d, *J* = 7.9, Ar*H*), 7.48 (1H, s, Ar*H*), 7.39 (1H, d, *J* = 7.9, Ar*H*), 4.74 (2H, s, CH_2N), 2.71 (2H, t, *J* = 7.7 ArCH_2CH$_2$), 2.53 (3H, s, CH_3C(O)), 1.61–1.56 (2H, m, ArCH$_2$CH_2), 1.31 2H, sextet, *J* = 7.4, CH_2CH$_3$), 0.90 (3H, t, *J* = 7.4, CH$_2$CH_3); ^{13}C NMR (150 MHz; DMSO-d_6); 170.2 (*C*(O)), 167.7 (*C*(O)), 149.6 (*Ar*), 142.1 (*Ar*), 129.0 (*Ar*), 128.5 (*Ar*), 124.3 (*Ar*), 123.6 (*Ar*), 47.9

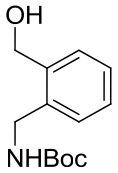
(*C*H_2N), 35.2 (Ar*C*H_2CH_2), 33.0 (ArCH_2*C*H_2), 24.6 (*C*H_3C(O)), 21.8 (*C*H_2CH_3), 13.8 (CH_2*C*H_3); HRMS (EI$^+$) found [M]$^+$ 231.1252; $C_{14}H_{17}NO_2$ requires 231.1259.

tert-Butyl 1-oxoisoindoline-2-carboxylate (286)[157]



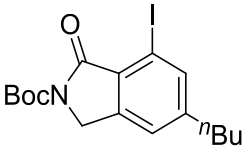
According to the procedure of Motherwell *et al*.[156]: Tin (41.7 g, 351 mmol) was added portionwise to a vigorously stirring suspension of phthalimide (20.0 g, 136 mmol) in AcOH (100 mL) and aq. HCl (50 mL, concentrated). The resultant suspension was heated at reflux for 2 h before being allowed to cool to RT. The reaction mixture was diluted with chloroform (100 mL) and the aq. extract washed with chloroform (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was washed with hot ether and recrystallized (hot EtOAc/ether) to give an impure sample isoindolin-1-one **285** as a yellow solid (13.0 g, *ca*. 80% purity by ^{1}H NMR). Then according to the modified procedure of Cativiela *et al*.[157]: Boc_2O (3.04 g, 13.9 mmol) and DMAP (68 mg, 0.56 mmol) were added to a stirring solution of isoindolin-1-one (800 mg, *ca.* 80% purity, *ca*. 4.8 mmol) in THF (45 mL) at RT. The reaction was stirred at RT for 16 h before the volatile components were removed *in vacuo* to give the crude product. This was purified by flash column chromatography (4:1 petrol 40–60 °C: EtOAc) to give the *isoindolinone* **286** as a white crystalline solid (832 mg, 3.57 mmol, 43% over 2 steps); m.p. 110–112 °C (literature 117–119 °C[157]); R_f = 0.25 (4:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}); 2980s (C-H), 1777s, 1742s, 1714s, 1618s, 1470s, 1454s; ^{1}H NMR (600 MHz; DMSO-d_6); 7.76 (1H, d, *J* = 7.6, Ar*H*), 7.72 (1H, t, *J* = 7.6, Ar*H*), 7.64 (1H, d, *J* = 7.6, Ar*H*), 7.53 (1H, t, *J* = 7.6, Ar*H*), 4.79 (2H, s, CH_2N), 1.52 (9H, s, C(CH_3)$_3$); ^{13}C NMR (150 MHz; DMSO-d_6) 165.9 (*C*(O)C), 149.7 (*C*(O)O), 141.5 (*Ar*), 133.7 (*Ar*), 130.8 (*Ar*), 128.4 (*Ar*), 124.0 (*Ar*), 123.9 (*Ar*), 81.9 (*C*Me$_3$), 49.1 (*C*H_2N), 27.8 (C(*C*H_3)$_3$); data in agreement with the literature.[157]

tert-Butyl 2-(hydroxymethyl)benzylcarbamate (288)



According to the modified procedure of Murata *et al.*[158]: A solution of $NaBH_4$ (105 mg, 2.78 mmol) in water (1.2 mL) was added dropwise to a stirring solution of isoindolinone **286** (100 mg, 0.429 mmol) in THF (4.0 mL) at 0 °C over 1 minute. The resulting mixture was stirred vigorously for 24 h with the reaction allowed to slowly reach RT. Amberlyst A-26 was added and the resulting mixture filtered. The filtrate was concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (5:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **288** as a white crystalline solid (66 mg, 0.28 mmol, 65%); m.p. 90–92 °C; R_f = 0.33 (2:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3352s (O-H), 2977s (C-H), 1686s (C=O), 1519s, 1454s; ^{1}H NMR (600 MHz; DMSO-d_6) a mixture of rotamers R_1 (major) and R_2 (minor) 7.37–7.35 (1H, m, Ar*H* R_1; 1H, m, Ar*H* R_2), 7.26 (1H, t, *J* = 6.0, N*H* R_1; 1H, t, *J* = 6.0, N*H* R_2), 7.23–7.20 (3H, m, Ar*H* R_1; 3H, m, Ar*H* R_2), 5.13 (1H, t, *J* = 5.4, O*H* R_1; 1H, t, *J* = 5.4, O*H* R_2), 4.54 (2H, d, *J* = 5.4, C*H*$_2$OH R_1; 2H, d, *J* = 5.4, C*H*$_2$OH R_2), 4.16 (2H, d, *J* = 6.0, C*H*$_2$N R_1; 2H, d, *J* = 6.0, C*H*$_2$N R_2) 3.36 (9H, s, C(C*H*$_3$)$_3$ R_1) 3.33 (9H, s, C(C*H*$_3$)$_3$ R_2); ^{13}C NMR (150 MHz; DMSO-d_6) 155.7 (*C*(O)), 139.4 (*Ar*), 137.1 (*Ar*), 127.1 (*Ar*), 126.9 (*Ar*), 126.8 (*Ar*), 126.5 (*Ar*), 77.8 (*C*Me$_3$), 60.6 (*C*H$_2$OH), 40.3 (*C*H$_2$N), 28.3 (C(*C*H$_3$)$_3$); HRMS (CI$^+$) found [M+H]$^+$ 238.1438; $C_{13}H_{20}NO_3$ requires 238.1443.

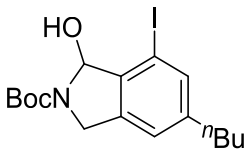
tert-Butyl 5-butyl-7-iodo-1-oxoisoindoline-2-carboxylate (289)



Boc_2O (55 mg, 0.25 mmol) and DMAP (1.5 mg, 0.012 mmol) were added to a stirring solution of isoindolinone **278** (40 mg, 0.13 mmol) in THF (2.0 mL) at RT. The resulting solution was stirred at RT for 16 h, after which a further quantity of Boc_2O (55 mg, 0.25 mmol) and DMAP (1.5 mg, 0.012 mmol) were added. After a further 3 h the reaction mixture was concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (10:1 petrol 40–60 °C:EtOAc) to give the *isoindolinone* **289** as

a colorless oil (48 mg, 0.12 mmol, 91%); R_f = 0.24 (10:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}), 2930s (C-H), 1777s (C=O), 1747s (C=O), 1712s (C=O), 1605s, 1456s; ^{1}H NMR (600 MHz; DMSO-d$_6$); 7.82 (1H, s, Ar*H*), 7.47 (1H, s, Ar*H*), 4.63 (2H, s, C*H*$_2$N), 2.64 (2H, t, *J* = 7.7, ArC*H*$_2$CH$_2$), 1.59–1.53 (2H, m, ArCH$_2$C*H*$_2$), 1.52 (9H, s, C(C*H*$_3$)$_3$) 1.30 (2H, sextet, *J* = 7.4, C*H*$_2$CH$_3$), 0.89 (3H, t, *J* = 7.4, CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$); 164.1 (*C*(O)C), 150.2 (*C*(O)O), 149.8 (*Ar*), 144.5 (*Ar*), 139.7 (*Ar*), 128.0 (*Ar*), 123.5 (*Ar*), 91.3 (*C*I), 82.0 (*C*Me$_3$), 47.3 (*C*H$_2$N), 34.4 (Ar*C*H$_2$CH$_2$), 32.7 (ArCH$_2$*C*H$_2$), 27.7 (C(*C*H$_3$)$_3$), 21.8 (*C*H$_2$CH$_3$), 13.7 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 416.0717; $C_{17}H_{23}INO_3$ requires 416.0723.

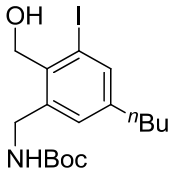
tert-Butyl 5-butyl-1-hydroxy-7-iodoisoindoline-2-carboxylate (290)



According to the modified procedure of Murata *et al.*[158]: A solution of NaBH$_4$ (19 mg, 0.49 mmol) in water (0.22 mL) was added dropwise to a stirring solution of isoindolinone **289** (32 mg, 0.077 mmol) in THF (0.70 mL) at 0 °C over 1 minute. The resulting mixture was stirred vigorously for 16 h with the reaction allowed to slowly reach RT. A further portion of NaBH$_4$ (19 mg, 0.49 mmol) was added to the reaction mixture at RT and the reaction was stirred vigorously of a further 24 h. Amberlyst A-26 was added and the resulting mixture filtered. The filtrate was concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (10:1 petrol 40–60 °C:EtOAc) to give hemiaminal **290** as a colorless oil (16 mg, 0.038 mmol, 50%); R_f = 0.20 (10:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2974s (C-H), 1755s, 1707s (C=O), 1456s; ^{1}H NMR (600 MHz; DMSO-d$_6$) a 50:50 mixture of rotamers R_1 and R_2; 7.55 (1H, s, Ar*H* R_1; 1H, s, Ar*H* R_2) 7.20 (1H, s, Ar*H* R_1 or R_2), 7.18 (1H, s, Ar*H* R_1 or R_2), 6.39 (1H, d, *J* = 8.0, O*H* R_1), 6.22 (1H, d, *J* = 8.3, O*H* R_2), 6.03 (1H, d, *J* = 8.0, C*H*O R_1), 5.94 (1H, d, *J* = 8.3, C*H*O R_2), 4.59–4.45 (2H, m, C*H*$_2$N R_1; 2H, m, C*H*$_2$N R_2), 2.56 (2H, t, *J* = 7.7, ArC*H*$_2$CH$_2$ R_1; 2H, t, *J* = 7.7, ArC*H*$_2$CH$_2$ R_2), 1.54–1.50 (2H, m, ArCH$_2$C*H*$_2$ R_1; 2H, m, ArCH$_2$C*H*$_2$ R_2), 1.47 (9H, s, C(C*H*$_3$)$_3$ R_1 or R_2), 1.46 (9H, s, C(C*H*$_3$)$_3$ R_1 or R_2), 1.28 (2H, sextet, *J* = 7.3, C*H*$_2$CH$_3$ R_1; 2H, sextet, *J* = 7.3, C*H*$_2$CH$_3$ R_2), 0.88 (3H, d, *J* = 7.3, CH$_2$C*H*$_3$ R_1; 3H, d, *J* = 7.3, CH$_2$C*H*$_3$ R_2); ^{13}C NMR (150 MHz; DMSO-d$_6$) a mixture of rotamers; 153.1 (*C*(O)), 153.0 (*C*(O)), 145.4 (*Ar*), 140.7 (*Ar*),

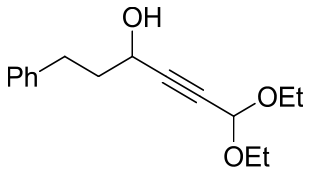
140.2 (*Ar*), 138.7 (*Ar*), 138.4 (*Ar*), 136.9 (*Ar*), 136.9 (*Ar*), 122.6 (*Ar*), 122.5 (*Ar*), 91.7 (*C*I), 85.6 (*C*HO), 85.6 (*C*HO), 79.4 (*C*Me$_3$), 79.2 (*C*Me$_3$), 50.7 (*C*H$_2$N), 50.4 (C*H*$_2$N), 34.1 (ArC*H*$_2$CH$_2$), 33.1 (ArCH$_2$*C*H$_2$), 28.1 (C(*C*H$_3$)$_3$), 21.7 (*C*H$_2$CH$_3$), 13.8 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 418.0870; $C_{17}H_{25}INO_3$ requires 418.0874.

***tert*-Butyl 5-butyl-2-(hydroxymethyl)-3-iodobenzylcarbamate (291)**



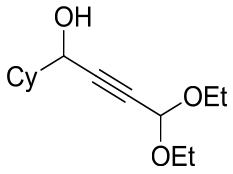
According to the modified procedure of Ohno *et al*.[159]: $LiBH_4$ (4.2 mg, 0.19 mmol) was added to a solution of isoindolinone **289** (32 mg, 0.077 mmol) and MeOH (3.7 mg, 0.12 mmol) in Et_2O (1.0 mL) at 0 °C. The resulting solution was stirred at RT for 90 minutes, after which a further portion of $LiBH_4$ (42 mg, 0.19 mmol) was added. The reaction was stirred at RT for a further 16 h before the reaction was diluted with aq. sat. NH_4Cl (10 mL) and Et_2O (10 mL). The aq. extract was washed with Et_2O (3 × 10 mL) and the combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. This was purified by flash column chromatography (8:1 petrol 40–60 °C:EtOAc) to give the *carbamate* **291** as a white crystalline solid (17 mg, 0.041 mmol, 53%); m.p. 78–76 °C; R_f = 0.11 (5:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}), 3353s (O-H, N-H), 2958s (C-H), 2925s (C-H), 2856s (C-H), 1687s (C=O) 1601s, 1507s, 1458s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 7.47 (1H, s, Ar*H*), 7.26 (1H, t, *J* = 5.9, N*H*), 7.09 (1H, s, Ar*H*), 5.01 (1H, t, *J* = 5.0, CH$_2$O*H*), 4.62 (2H, d, *J* = 5.0, C*H*$_2$OH), 4.28 (2H, d, *J* = 5.9, C*H*$_2$N), 2.51–2.48 (2H, m, ArC*H*$_2$CH$_2$ and solvent peak), 1.49 (2H, quintet, *J* = 7.4, ArCH$_2$C*H*$_2$), 1.39 (9H, s, C(C*H*$_3$)$_3$), 1.27 (2H, sextet, *J* = 7.4, C*H*$_2$CH$_3$), 0.87 (3H, t, *J* = 7.4, CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$); 155.7 (*C*(O)), 143.8 (*Ar*), 140.4 (*Ar*), 137.7 (*Ar*), 137.4 (*Ar*), 127.8 (*Ar*), 102.5 (*C*I), 78.0 (*C*Me$_3$), 64.8 (*C*H$_2$OH), 42.7 (*C*H$_2$N), 33.9 (Ar*C*H$_2$CH$_2$), 32.9 (ArCH$_2$*C*H$_2$), 28.2 (C(*C*H$_3$)$_3$), 21.6 (*C*H$_2$CH$_3$), 13.8 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 420.1027; $C_{17}H_{27}INO_3$ requires 420.1030.

6,6-Diethoxy-1-phenylhex-4-yn-3-ol (316a)[190]



Prepared from 3-phenylpropanal (8.8 mL, 9.0 g, 90% purity by weight, 60 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (4:1 petrol 40–60 °C:EtOAc) to give the propargylic alcohol **316a** as a colorless oil (12.8 g, 48.8 mmol, 81%); R_f = 0.33 (4:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3426s (O-H), 2976s (C-H), 1454s; ^{1}H NMR (500 MHz; $CDCl_3$); 7.30–7.25 (2H, m, Ar*H*), 7.21–7.18 (3H, m, Ar*H*), 5.31 (1H, s, C*H*(OEt)$_2$), 4.45–4.40 (1H, m, C*H*OH), 3.78–3.71 (2H, m, C(OC*H*H')$_2$), 3.68–3.57 (2H, m, C(OCH*H*')$_2$), 2.80 (2H, t, *J* = 7.8, PhC*H*$_2$), 2.08–2.01 (2H, m, C*H*$_2$COH), 1.89 (1H, d, *J* = 5.1, O*H*), 1.24 (6H, t, *J* = 7.1, C*H*$_3$); ^{13}C NMR (125 MHz; $CDCl_3$) 141.3 (*Ar*), 128.6 (*Ar*), 128.5 (*Ar*), 126.1 (*Ar*), 91.4 (*C*(OEt)$_2$), 86.7 (*C*≡C), 80.3 (*C*≡C), 61.3 (*C*OH), 61.1 (O*C*H$_2$), 61.0 (O*C*H$_2$), 39.1 (Ph*C*H$_2$), 31.5 (*C*H$_2$COH), 15.2 (CH$_2$*C*H$_3$); data in accordance with the literature.[190]

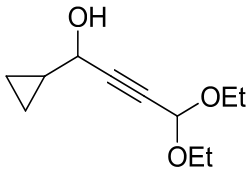
1-Cyclohexyl-4,4-diethoxybut-2-yn-1-ol (316b)[190]



Prepared from cyclohexanecarbaldehyde (2.0 mL, 1.3 g, 14.0 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 50% EtOAc:cyclohexane) to give the propargylic alcohol **316b** as a colorless oil (2.39 g, 9.94 mmol, 86%); R_f = 0.29 (10:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3416s br. (O-H), 2925s (C-H), 1450s; ^{1}H NMR (600 MHz; $CDCl_3$) 5.28 (1H, s, C*H*(OEt)$_2$), 4.18 (1H, d, *J* = 6.0, C*H*OH), 3.74–3.68 (2H, m, OC*H*H'), 3.59–3.53 (2H, m, OCH*H*'), 2.20 (br. s, CHO*H*), 1.89–1.79 (2H, m, CHC*H*H'), 1.76–1.72 (2H, m, CHCH$_2$C*H*H'), 1.67–1.62 (1H, m, CHCH$_2$CH$_2$C*H*H'), 1.57–1.51 (1H, m, C*H*CH$_2$), 1.26–1.18 (8H, m, 2 × C*H*$_3$, 2 × CHCH$_2$CH*H*'), 1.16–0.99 (3H, m, 2 × CHCH*H*', CHCH$_2$CH$_2$CH*H*'); ^{13}C NMR (150 MHz; $CDCl_3$) 91.3 (*C*H(OEt)$_2$), 85.7 (*C*≡C), 80.9 (*C*≡C), 67.0 (*C*HOH), 61.0 (O*C*H$_2$), 60.9 (O*C*H$_2$), 43.9 (*C*HCH$_2$), 28.6 (CH*C*H$_2$), 28.2 (CH*C*H$_2$), 26.4

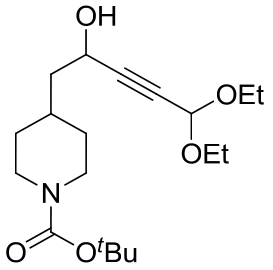
($CHCH_2CH_2CH_2$), 25.9 ($CHCH_2CH_2$), 25.9 ($CHCH_2CH_2$), 15.2 (CH_2CH_3); data in accordance with the literature.[190]

1-Cyclopropyl-4,4-diethoxybut-2-yn-1-ol (316c)[190]



Prepared from cyclopropanecarbaldehyde (0.90 mL, 0.84 g, 12 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 50% EtOAc:cyclohexane) to give the propargylic alcohol **316c** as a colorless oil (1.97 g, 9.94 mmol, 83%); R_f = 0.29 (3:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 3403s br. (O-H), 2977s (C-H), 1444m; ^{1}H NMR (400 MHz; $CDCl_3$) 5.32–5.29 (1H, m, C*H*$(OEt)_2$), 4.27–4.21 (1H, m, C*H*OH), 3.78–3.69 (2H, m, OC*H*H'), 3.64–3.54 (2H, m, OCH*H*'), 2.40–1.93 (1H, m, O*H*); 1.31–1.21 (7H, m, CH_2CH_3, C*H*$(CH_2)_2$), 0.63–0.42 (4H, m, CH(C$H_2)_2$); ^{13}C NMR (100 MHz; $CDCl_3$) 89.6 (*C*H$(OEt)_2$), 82.7 (*C*≡C), 78.7 (*C*≡C), 63.9 (*C*HOH), 59.3 (O*C*H_2), 59.2 (O*C*H_2), 15.3 (CH_2CH_3), 13.4 (*C*H$(CH_2)_2$), 1.6 (CH(*C*$H_2)_2$); data in accordance with the literature.[190]

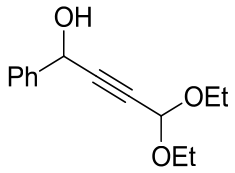
***tert*-Butyl 4-(5,5-diethoxy-2-hydroxypent-3-yn-1-yl)piperidine-1-carboxylate (316d)**



Prepared from a solution of *tert*-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (1.50 g, 6.60 mmol) in anhydrous THF (4.0 mL) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 100% heptane:TBME) to the *propargylic alcohol* **316d** as a colorless oil (1.67 g, 4.70 mmol, 71%); R_f = 0.47 (1:1 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3417s br. (O-H), 2929s (C-H), 1693s (C=O), 1669s (C=O), 1424s; ^{1}H NMR (400 MHz; $CDCl_3$) 5.31 (1H, s, (C*H*$(OEt)_2$), 4.54 (1H, q, *J* = 5.9, C*H*OH), 4.10 (2H, br. s, NC*H*H'), 3.79–3.71 (2H, m, OC*H*H'), 3.64–3.57 (2H, m, OCH*H*'), 2.71 (2H, br. t, NCH*H*'), 1.89 (1H, m, O*H*), 1.76–1.62 (5H, m, OCHCH_2C*H*(C*H*H')$_2$), 1.47 (9H, s, C(C$H_3)_3$), 1.26 (6H, t, CH_2CH_3), 1.20–1.12 (2H, m,

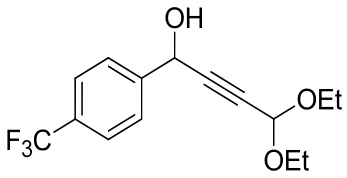
OCHCH$_2$CH(CH*H*')$_2$); ^{13}C NMR (100 MHz; CDCl$_3$) 154.8 (*C*(O)), 91.3 (*C*H(OEt)$_2$), 86.3 (*C*≡C), 80.4 (*C*≡C), 79.3 (*C*(CH$_3$)$_3$), 61.0 (O*C*H$_2$), 60.9 (O*C*H$_2$), 60.0 (*C*HOH), 43.05 (N*C*H$_2$, OCH*C*H$_2$), 32.5 (OCHCH$_2$*C*H), 32.3 (OCHCH$_2$CH(*C*H$_2$)(CH$_2$)'), 31.8 (OCHCH$_2$CH(CH$_2$)(*C*H$_2$)'), 28.5 (C(*C*H$_3$)$_3$), 15.1 (CH$_2$*C*H$_3$); HRMS (ESI$^+$) found [M+Na]$^+$ 378.2202; $C_{19}H_{33}NNaO_5$ requires 378.2256.

4,4-Diethoxy-1-phenylbut-2-yn-1-ol (316e)[190]



Prepared from benzaldehyde (4.9 mL, 5.0 g, 47 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (7:1 40–60 °C:EtOAc) to give the propargylic alcohol **316e** as a colorless oil (10.5 g, 44.6 mmol, 95%); R_f = 0.33 (5:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3317s br. (O-H), 2977s (C-H), 1493m, 1455s; ^{1}H NMR (400 MHz; CDCl$_3$) 7.57–7.54 (2H, m, Ar*H*), 7.43–7.33 (3H, m, Ar*H*), 5.83 (1H, s, C*H*(OEt)$_2$), 5.55 (1H, d, *J* = 6.2, C*H*OH), 3.81–3.73 (2H, m, OC*H*H'), 3.67–3.58 (2H, m, OCH*H*'), 2.43 (1H, d, *J* = 6.2, O*H*), 1.25 (6H, t, *J* = 7.1, CH$_2$C*H*$_3$); ^{13}C NMR (125 MHz; CDCl$_3$) 140.1 (*Ar*), 128.7 (*Ar*), 128.5 (*Ar*), 126.7 (*Ar*), 91.4 (*C*H(OEt)$_2$), 85.2 (*C*≡C), 82.0 (*C*≡C), 64.5 (*C*HOH), 61.1 (O*C*H$_2$), 61.0 (O*C*H$_2$), 15.1 (CH$_2$*C*H$_3$); data in accordance with the literature.[190]

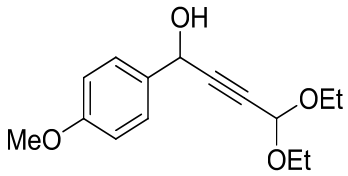
4,4-Diethoxy-1-(4-(trifluoromethyl)phenyl)but-2-yn-1-ol (316f)[190]



Prepared from 4-(trifluoromethyl)benzaldehyde (1.6 mL, 2.0 g, 12 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 50% EtOAc:cyclohexane) to give the propargylic alcohol **316f** as a colorless oil (2.88 g, 9.94 mmol, 79%); R_f = 0.22 (3:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 3408s br. (O-H), 2981s (C-H), 1620s, 1416s; ^{1}H NMR (400 MHz; CDCl$_3$) 7.69–7.64 (4H, m, Ar*H*), 5.60 (1H, d, *J* = 5.9, C*H*OH), 5.37 (1H, s, C*H*(OEt)$_2$), 3.80–3.72 (2H, m, OC*H*H'), 3.66–3.58 (2H, m, OCH*H*'), 2.66–1.63 (1H, m, CO*H*), 1,26 (6H, t, *J* = 7.0, CH$_2$C*H*$_3$); ^{13}C NMR

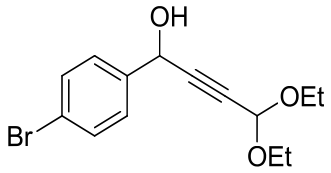
(100 MHz; $CDCl_3$) 143.7 (*Ar*), 130.6 (q, $J_{C\text{-}F}$ = 30.0, *Ar*), 126.9 (*Ar*), 125.6 (q, $J_{C\text{-}F}$ = 3.5, *Ar*), 124.0 (q, $J_{C\text{-}F}$ = 272.2, *C*F_3), 91.2 (*C*H(OEt)$_2$), 84.2 (*C*≡C), 82.6 (*C*≡C), 63.7 (*C*HOH), 61.1 (O*C*H_2), 61.1 (O*C*H_2), 15.0 (CH_2*C*H_3); data in accordance with the literature.[190]

4,4-Diethoxy-1-(4-methoxyphenyl)but-2-yn-1-ol (316g)[190]



Prepared from 4-methoxybenzaldehyde (1.4 mL, 1.6 g, 11 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 50% EtOAc:cyclohexane) to give the propargylic alcohol **316g** as a yellow oil (2.92 g, 11.1 mmol, 96%); R_f = 0.18 (3:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 3423s br. (O-H), 2976s (C-H), 1611s, 1511s; ^{1}H NMR (400 MHz; DMSO-d_6) 7.43–733 (2H, m, Ar*H*), 6.96–9.88 (2H, m, Ar*H*), 5.97 (1H, br. s, CHO*H*), 5.37 (1H, br. s, C*H*OH), 5.37 (1H, s, C*H*(OEt)$_2$), 3.75 (3H, s, OCH_3), 3.67–3.56 (2H, m, OC*H*H'), 3.55–3.45 (2H, m, OCH*H*'), 1.13 (6H, t, *J* = 7.1, CH_2CH_3); ^{13}C NMR (100 MHz; DMSO-d_6) 159.2 (*Ar*), 134.3 (*Ar*), 128.1 (*Ar*), 114.1 (*Ar*), 91.2 (*C*H(OEt)$_2$), 87.2 (*C*≡C), 80.7 (*C*≡C), 62.3 (*C*HOH), 60.6 (O*C*H_2), 55.6 (O*C*H_3), 15.4 (CH_2*C*H_3); data in accordance with the literature.[190]

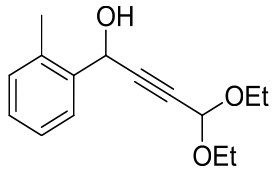
1-(4-Bromophenyl)-4,4-diethoxybut-2-yn-1-ol (316h)[190]



Prepared from a solution of 4-bromobenzaldehyde (2.15 g, 11.9 mmol) in anhydrous THF (12 mL) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 100% EtOAc:cyclohexane) to give the propargylic alcohol **316h** as a colorless oil (3.01 g, 9.61 mmol, 83%); R_f = 0.69 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 3410s br. (O-H), 2978s (C-H), 1486s; ^{1}H NMR (400 MHz; $CDCl_3$) 7.55–7.51 (2H, m, Ar*H*), 7.45–7.41 (2H, m, Ar*H*), 5.51 (1H, d, *J* = 6.0, C*H*OH), 5.36 (1H, s, C*H*(OEt)$_2$), 3.80–3.71 (2H, m, OC*H*H'), 3.66–3.58 (2H, m, OCH*H*'), 2.40 (1H, d, *J* = 6.0, CO*H*), 1.26 (3H, t, *J* = 7.1, CH_2CH_3), 1.26 (3H, t, *J* = 7.1, CH_2CH_3); ^{13}C NMR (100 MHz;

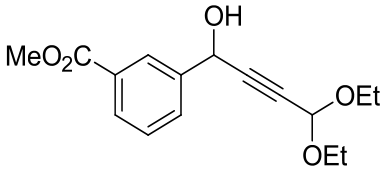
$CDCl_3$) 138.4 (*Ar*), 131.7 (*Ar*), 128.3 (*Ar*), 122.5 (*Ar*), 91.3 (*C*H(OEt)$_2$), 84.4 (*C*≡C), 82.4 (*C*≡C), 63.8 (*C*HOH), 61.1 (O*C*H$_2$), 61.0 (O*C*H$_2$), 15.1 (CH$_2$*C*H$_3$); data in accordance with the literature.[190]

4,4-Diethoxy-1-(*o*-tolyl)but-2-yn-1-ol (316i)



Prepared from 2-methylbenzaldehyde (1.3 mL, 1.4 g, 11 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 100% EtOAc:cyclohexane) to give the *propargylic alcohol* **316i** as a colorless oil (2.58 g, 10.4 mmol, 92%); R_f = 0.24 (3:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 3422s br. (O-H), 2977s (C-H), 1487s, 1460s; ^{1}H NMR (400 MHz; $CDCl_3$) 7.68–7.63 (1H, m, Ar*H*), 7.28–7.18 (3H, m, Ar*H*), 5.70 (1H, dd, *J* = 6.0, 1.2, C*H*OH), 5.37 (1H, d, *J* = 1.2, C*H*(OEt)$_2$), 3.81–3.72 (2H, m, OC*H*H'), 3.67–3.58 (2H, m, OCH*H*'), 2.46 (3H, s, ArC*H*$_3$), 2.20 (1H, d, *J* = 6.0, O*H*), 1.26 (3H, t, *J* = 7.1, CH$_2$C*H*$_3$), 1.25 (3H, t, *J* = 7.1, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) 137.0 (*Ar*), 136.0 (*Ar*), 130.8 (*Ar*), 128.6 (*Ar*), 126.6 (*Ar*), 126.2 (*Ar*), 91.4 (*C*H(OEt)$_2$), 84.7 (*C*≡C), 82.0 (*C*≡C), 62.3 (*C*HOH), 61.0 (O*C*H$_2$), 61.0 (O*C*H$_2$), 18.9 (ArCH$_3$), 15.1 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M]$^+$ 248.1409; $C_{15}H_{20}O_3$ requires 248.1412.

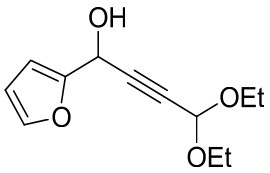
Methyl 3-(4,4-diethoxy-1-hydroxybut-2-yn-1-yl)benzoate (316j)[190]



Prepared from a solution of methyl 3-formylbenzoate (1.31 g, 7.98 mmol) in anhydrous THF (8.0 mL) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give the propargylic alcohol **316j** as a colorless oil (1.83 g, 6.26 mmol, 78%); R_f = 0.71 (3:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 3433s br. (O-H), 2887s (C-H), 1721s (C=O), 1481s; ^{1}H NMR (400 MHz; MeOH-d_4) 8.22 (1H, s, Ar*H*), 7.98 (1H, d, *J* = 7.8, Ar*H*), 7.77 (1H, d, *J* = 7.8, Ar*H*), 7.51 (1H, t, *J* = 7.8, Ar*H*), 5.56 (1H, s, C*H*OH), 5.37 (1H, s, C*H*(OEt)$_2$), 3.93 (3H, s, OC*H*$_3$), 3.80–3.70 (2H, m, OC*H*H'), 3.67–3.56 (2H, m, OCH*H*'), 1.21 (6H, t, *J* = 7.1 CH$_2$C*H*$_3$);

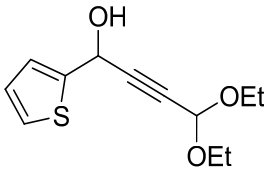
^{13}C NMR (100 MHz; MeOH-d$_4$) 166.8 (*C*(O)), 141.8 (*Ar*), 131.0 (*Ar*), 130.2 (*Ar*), 128.8 (*Ar*), 128.4 (*Ar*), 127.3 (*Ar*), 91.3 (*C*H(OEt)$_2$), 85.0 (*C*≡C), 81.1 (*C*≡C), 62.8 (*C*HOH), 60.7 (O*C*H$_2$), 60.7 (O*C*H$_2$), 51.3 (O*C*H$_3$), 14.0 (CH$_2$*C*H$_3$); data in accordance with the literature.[190]

4,4-Diethoxy-1-(furan-2-yl)but-2-yn-1-ol (316k)[190]



Prepared from furfural (0.96 mL, 1.1 g, 12 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 50% EtOAc:cyclohexane) to give the propargylic alcohol **316k** as a yellow oil (2.23 g, 9.96 mmol, 86%); R_f = 0.30 (3:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 3411s br. (O-H), 2978s (C-H); ^{1}H NMR (400 MHz; CDCl$_3$) 7.43–7.42 (1H, m, Ar*H*), 6.47 (1H, d, *J* = 3.2, Ar*H*), 6.38–6.36 (1H, m, Ar*H*), 5.53 (1H, d, *J* = 6.9, C*H*OH), 5.37–5.36 (1H, m, C*H*(OEt)$_2$), 3.82–3.73 (2H, m, OC*H*H'), 3.68–3.60 (2H, m, OCH*H*'), 2.69–1.50 (1H, m, O*H*), 1.25 (6H, t, *J* = 6.8, C*H*$_3$); ^{13}C NMR (100 MHz; CDCl$_3$) 152.4 (*Ar*), 143.1 (*Ar*), 110.4 (*Ar*), 108.0 (*Ar*), 91.2 (*C*H(OEt)$_2$), 82.6 (*C*≡C), 81.2 (*C*≡C), 61.1 (O*C*H$_2$), 61.0 (O*C*H$_2$), 58.0 (*C*HOH), 15.0 (CH$_2$*C*H$_3$); data in accordance with the literature.[190]

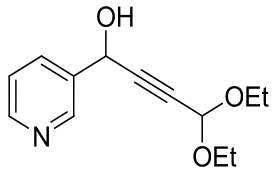
4,4-Diethoxy-1-(thiophen-2-yl)but-2-yn-1-ol (316l)[190]



Prepared from thiophene-2-carbaldehyde (1.6 mL, 1.9 g, 17 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give the propargylic alcohol **316l** as a yellow oil (2.00 g, 8.32 mmol, 49%); R_f = 0.61 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 3403s br. (O-H), 2926s (C-H); ^{1}H NMR (400 MHz; CDCl$_3$) 7.33–7.31 (1H, m Ar*H*), 7.21–7.17 (1H, m, Ar*H*), 7.00–6.98 (1H, m Ar*H*), 5.74 (1H, d, *J* = 6.9, C*H*OH), 5.37 (1H, s, C*H*(OEt)$_2$), 3.83–3.74 (2H, m, OC*H*H'), 3.67–3.58 (2H, m, OCH*H*'), 2.69 (1H, d, *J* = 6.9, O*H*), 1.26 (6H, t, *J* = 7.1, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz; CDCl$_3$) 143.9 (*Ar*), 126.8 (*Ar*), 126.2 (*Ar*),

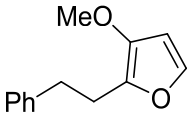
125.7 (*Ar*), 91.2 (*C*H(OEt)$_2$), 84.3 (*C*≡C), 81.4 (*C*≡C), 61.1 (O*C*H$_2$), 61.0 (O*C*H$_2$), 60.1 (*C*HOH), 15.1 (CH$_2$*C*H$_3$); data in accordance with the literature.[190]

4,4-Diethoxy-1-(pyridin-3-yl)but-2-yn-1-ol (316m)



Prepared from nicotinaldehyde (1.1 mL, 1.3 g, 12 mmol) according to the General Alkynylation Procedure and purified by flash column chromatography (0 to 100% cyclohexane: EtOAc) to give the *propargylic alcohol* **316m** as a yellow oil (1.93 g, 8.20 mmol, 70%); R_f = 0.40 (40:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 3160s br. (O-H), 2977s (C-H), 1427s; ^{1}H NMR (400 MHz; DMSO-d$_6$) 8.65 (1H, d, *J* = 1.8, Ar*H*), 8.53 (1H, dd, *J* = 4.9, 1.8, Ar*H*), 7.84 (1H, dt, 7.8, 1.8, Ar*H*), 7.42 (1H, dd, *J* = 7.8, 4.9, Ar*H*), 6.31 (1H, d, *J* = 6.1, CHO*H*), 5.55 (1H, d, *J* = 6.1, C*H*OH), 5.37 (1H, s, C*H*(OEt)$_2$), 3.66–3.58 (2H, m, OC*H*H'), 3.55–3.47 (2H, m, OCH*H*'), 1.13 (6H, t, *J* = 7.1, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz; DMSO-d$_6$) 148.9 (*Ar*), 147.8 (*Ar*), 137.1 (*Ar*), 134.0 (*Ar*), 123.5 (*Ar*), 90.7 (*C*H(OEt)$_2$), 85.6 (*C*≡C), 81.0 (*C*≡C), 60.8 (*C*HOH), 60.3 (O*C*H$_2$), 60.2 (O*C*H$_2$), 14.9 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 236.1281; $C_{14}H_{17}NO_3$ requires 236.1287.

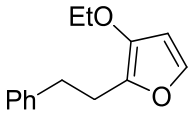
3-Methoxy-2-phenethylfuran (318)[190]



A solution of [PPh$_3$AuNTf$_2$]$_2$PhMe (30 mg, 0.019 mmol, 1.0 mol%, 2.0 mol% [Au]) in MeOH (4.8 mL) was added dropwise to a stirring solution of propargylic alcohol **316a** (500 mg, 1.91 mmol) in MeOH (4.8 mL) at RT. The resulting solution was stirred for 16 h before being filtered through a silica plug, eluting with TBME. The filtrate was concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (0 to 10% petrol 30–40 °C: TBME) to give the furan **318** as a colorless oil (266 mg, 1.32 mmol, 69%); R_f = 0.29 (40:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2935s (C-H), 1637s, 1496s, 1454s 1410s; ^{1}H NMR (600 MHz; CDCl$_3$) 7.28–7.26 (2H, m, Ar*H*), 7.20–7.16 (3H, m, Ar*H*), 7.14 (1H, d, *J* = 2.1, Ar*H*), 6.26 (1H, d, *J* = 2.1, Ar*H*), 3.59 (3H, s, OC*H*$_3$), 2.94–2.86 (4H, m, PhC*H*$_2$C*H*$_2$); ^{13}C NMR (150 MHz; CDCl$_3$) 143.7

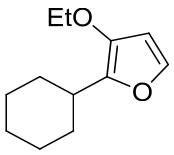
(*Ar*), 141.6 (*Ar*), 139.2 (*Ar*), 139.2 (*Ar*), 128.6 (*Ar*), 128.4 (*Ar*), 126.0 (*Ar*), 103.3 (*Ar*), 59.6 (O*C*H$_3$), 34.4 (*C*H$_2$) 27.2 (*C*H$_2$); data in accordance with the literature.[190]

3-Ethoxy-2-phenethylfuran (325a)[190]



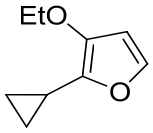
Prepared according to the General Furan Procedure from propargylic alcohol **316a** (500 mg, 1.91 mmol) in EtOH (0.50 M) to give the furan **325a** as a colorless oil (737 mg, 3.41 mmol, 45%); R_f = 0.72 (10:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2927s (C-H), 1635s, 1495s, 1453s, 1420s; ^{1}H NMR (400 MHz; MeOH-d$_4$) 7.27–7.09 (6H, m, Ar*H*), 6.28 (1H, d, *J* = 2.0, Ar*H*), 3.74 (2H, q, *J* = 7.1, OC*H*$_2$), 2.93–2.81 (4H, m, C*H*$_2$C*H*$_2$Ph), 1.19 (3H, t, *J* = 7.1, CH$_2$C*H*$_3$); ^{13}C NMR (125 MHz; CDCl$_3$) 142.4 (*Ar*), 141.3 (*Ar*), 139.3 (*Ar*), 139.0 (*Ar*), 128.1 (*Ar*), 127.8 (*Ar*), 125.5 (*Ar*), 103.6 (*Ar*), 67.4 (O*C*H$_2$), 33.9 (*C*H$_2$), 26.6 (*C*H$_2$), 14.0 (CH$_2$*C*H$_3$);. data in accordance with the literature.[190]

2-Cyclohexyl-3-ethoxyfuran (325b)



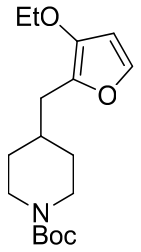
Prepared according to the General Furan Procedure from propargylic alcohol **316b** (0.500 g, 2.08 mmol) in EtOH (2.0 M) to give the *furan* **425b** as a colorless oil (273 mg, 1.41 mmol, 68%); R_f= 0.33 (40:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2927s (C-H), 1627s; ^{1}H NMR (600 MHz; CDCl$_3$) 7.09 (1H, s, Ar*H*), 7.08 (1H, s, Ar*H*), 3.91 (2H, q, *J* = 7.0, OC*H*$_2$), 2.70 (1H, tt, *J* = 11.7, 3.2, ArC*H*), 1.84–1.76 (4H, m, 2 × CHC*H*H', 2 × CHCH$_2$C*H*H'), 1.71–1.66 (1H, m, C*H*H'CH$_2$CH$_2$CH), 1.58–1.51 (2H, m, CHCH*H*'), 1.37–1.29 (5H, m, CH$_2$C*H*$_3$; 2 × CHCH$_2$CH*H*'), 1.28–1.23 (1H, m, CH*H*'CH$_2$CH$_2$CH); ^{13}C NMR (150 MHz; CDCl$_3$) 145.0 (*Ar*), 140.6 (*Ar*), 138.6 (*Ar*), 140.2 (*Ar*), 68.1 (O*C*H$_2$), 35.3 (*C*HCH$_2$), 31.3 (CH*C*H$_2$), 26.5 (CHCH$_2$*C*H$_2$), 26.1 (CHCH$_2$CH$_2$*C*H$_2$), 15.4 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 195.1389; $C_{12}H_{19}O_2$ requires 195.1385.

2-Cyclopropyl-3-ethoxyfuran (325c)[190]



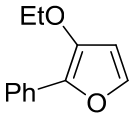
Prepared according to the General Furan Procedure from propargylic alcohol **316c** (250 mg, 1.26 mmol) in EtOH (2.0 M) to give the furan **325c** as a colorless oil (56 mg, 0.368 mmol, 29%); R_f = 0.78 (10:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2991s (C-H), 1666s, 1600s, 1432s; ^{1}H NMR (400 MHz; DMSO-d$_6$) 7.24 (1H, d, *J* = 2.0, Ar*H*), 6.41 (1H, d, *J* = 2.0, Ar*H*), 3.91 (2H, q, *J* = 7.1, OC*H*$_2$), 1.86–1.79 (1H, m, C*H*(CH$_2$)$_2$), 1.24 (3H, t, *J* = 7.1, CH$_2$C*H*$_3$), 0.84–0.80 (2H, m, CH(C*H*H')$_2$), 0.73–0.69 (2H, m, CH(CH*H*')$_2$); ^{13}C NMR (100 MHz; DMSO-d$_6$) 142.0 (*Ar*), 139.1 (*Ar*), 128.6 (*Ar*), 104.5 (*Ar*), 66.8 (O*C*H$_2$), 14.9 (CH$_2$*C*H$_3$), 6.3 (*C*H(CH$_2$)$_2$), 5.3 (CH(*C*H$_2$)$_2$); data in accordance with the literature.[190]

***tert*-Butyl 4-((3-ethoxyfuran-2-yl)methyl)piperidine-1-carboxylate (325d)**



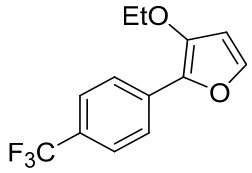
Prepared according to the General Furan Procedure from propargylic alcohol **316d** (500 mg, 1.41 mmol) in EtOH (1.0 M) to give the *furan* **325d** as a colorless oil (335 mg, 1.08 mmol, 77%); R_f = 0.34 (10:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2930s (C-H), 1693s (C=O), 1422m; ^{1}H NMR (400 MHz; DMSO-d$_6$) 7.20 (1H, d, *J* = 2.0, Ar*H*), 6.35 (1H, d, *J* = 2.0, Ar*H*), 4.07–4.01 (2H, m, NC*H*H'), 3.95 (2H, q, *J* = 7.1, OC*H*$_2$), 2.83–2.68 (2H, m, NCH*H*'), 2.53 (2H, d, *J* = 6.9, ArC*H*$_2$), 1.86–1.75 (1H, m, ArCH$_2$C*H*), 1.67–1.61 (2H, m, CH(C*H*H')$_2$), 1.47 (9H, s, C(C*H*$_3$)$_3$), 1.31 (3H, t, *J* = 7.1, CH$_2$C*H*$_3$), 1.19–1.07 (2H, m, CH(CH*H*')$_2$); ^{13}C NMR (100 MHz; DMSO-d$_6$) 156.6 (*C*(O)), 144.4 (*Ar*), 140.6 (*Ar*), 139.7 (*Ar*), 104.6 (*Ar*), 80.9 (*C*Me$_3$), 68.6 (O*C*H$_2$), 36.9 (ArCH$_2$*C*H), 33.0 (CH(*C*H$_2$)$_2$), 32.5 (Ar*C*H$_2$), 28.7 (C(*C*H$_3$)$_3$), 15.5 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 310.2012; $C_{17}H_{27}NO_4$ requires 310.2018.

3-Ethoxy-2-phenylfuran (325e)[190]



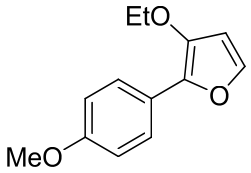
Prepared according to the General Furan Procedure from propargylic alcohol **316e** (2.00 g, 8.54 mmol) in EtOH (2.0 M) to give the furan **325e** as a colorless oil (910 mg, 4.83 mmol, 57%); R_f = 0.33 (40:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2980s (C-H), 1612s, 1510s, 1427s; ^{1}H NMR (600 MHz; $CDCl_3$) 7.81 (2H, d, *J* = 7.7, Ar*H*), 7.37 (2H, t, *J* = 7.7, Ar*H*), 7.27 (1H, d, *J* = 1.6, Ar*H*), 7.17 (1H, t, *J* = 7.7, Ar*H*), 6.40 (1H, d, *J* = 1.6, Ar*H*), 4.10 (2H, q, *J* = 7.0, OC*H*$_2$), 1.44 (3H, t, *J* = 7.0, CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz; $CDCl_3$) 144.4 (*Ar*), 140.2 (*Ar*), 136.9 (*Ar*), 131.1 (*Ar*), 128.5 (*Ar*), 125.8 (*Ar*), 123.1 (*Ar*), 104.1 (*Ar*), 67.3 (O*C*H$_2$), 15.4 (CH$_2$*C*H$_3$); data in accordance with the literature.[190]

3-Ethoxy-2-(4-(trifluoromethyl)phenyl)furan (325f)[190]



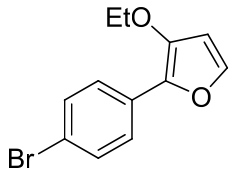
Prepared according to the General Furan Procedure from propargylic alcohol **316f** (500 mg, 1.65 mmol) in EtOH (2.0 M) to give the furan **325f** as a colorless oil (357 mg, 1.39 mmol, 84%); R_f = 0.50 (10:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2985s (C-H), 1614s; ^{1}H NMR (600 MHz; MeOH-d_4) 7.92 (2H, d, *J* = 8.3, Ar*H*), 7.34 (2H, d, *J* = 8.3, Ar*H*), 7.47 (1H, d, *J* = 2.1, Ar*H*), 6.62 (1H, d, *J* = 2.1, Ar*H*), 4.19 (2H, q, *J* = 7.1, OC*H*$_2$), 1.46 (3H, t, *J* = 7.1, CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz; MeOH-d_4) 146.5 (*Ar*), 141.7 (*Ar*), 134.8 (*Ar*), 134.4 (q, $J_{C\text{-}F}$ = 1.3, *Ar*), 126.5 (q, $J_{C\text{-}F}$ = 32.3, *Ar*), 124.9 (q, $J_{C\text{-}F}$ = 3.9, *Ar*), 124.5 (q, $J_{C\text{-}F}$ = 271.0, *C*F$_3$), 122.3 (*Ar*), 103.6 (*Ar*), 66.9 (O*C*H$_2$), 14.0 (CH$_2$*C*H$_3$); data in accordance with the literature.[190]

3-Ethoxy-2-(4-methoxyphenyl)furan (325g)[190]



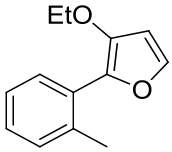
Prepared according to the General Furan Procedure from propargylic alcohol **316g** (500 mg, 1.89 mmol) in EtOH (0.50 M) to give the furan **325g** as a colorless oil (334 mg, 1.53 mmol, 81%); R_f = 0.48 (10:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2980s (C-H), 1606s, 1520s, 1431s; ^{1}H NMR (400 MHz; MeOH-d$_4$) 7.72–7.69 (2H, m, Ar*H*), 7.30 (1H, d, *J* = 2.2, Ar*H*), 7.95–7.91 (2H, m, Ar*H*), 6.51 (1H, d, *J* = 2.2, Ar*H*), 4.08 (2H, q, *J* = 7.0, OC*H*$_2$), 3.90 (3H, s, OC*H*$_3$), 1.40 (3H, t, *J* = 7.0, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz; MeOH-d$_4$) 157.9 (*Ar*), 142.7 (*Ar*), 139.3 (*Ar*), 136.9 (*Ar*), 128.5 (*Ar*), 124.0 (*Ar*), 113.5 (*Ar*), 103.8 (*Ar*), 66.8 (O*C*H$_2$), 54.3 (O*C*H$_3$), 14.2 (CH$_2$*C*H$_3$); data in accordance with the literature.[190]

2-(4-Bromophenyl)-3-ethoxyfuran (325h)



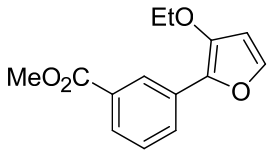
Prepared according to the General Furan Procedure from propargylic alcohol **316h** (500 mg, 1.60 mmol) in EtOH (2.0 M) to give the *furan* **325h** as a colorless oil (334 mg, 1.25 mmol, 78%); R_f = 0.57 (10:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2980s (C-H), 1669m, 1612s, 1504s, 1431s; ^{1}H NMR (400 MHz; DMSO-d$_6$) 7.67–7.65 (5H, m, Ar*H*), 6.75 (1H, d, *J* = 2.0, Ar*H*), 4.10 (2H, q, *J* = 6.8, OC*H*$_2$), 1.35 (3H, t, *J* = 6.8, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz; DMSO-d$_6$) 145.1 (*Ar*), 141.9 (*Ar*), 134.2 (*Ar*), 131.6 (*Ar*), 129.6 (*Ar*), 124.0 (*Ar*), 118.1 (*Ar*), 104.8 (*Ar*), 66.8 (O*C*H$_2$), 14.9 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 265.9942; C$_{12}$H$_{12}$^{79}BrO$_2$ requires 265.9945.

3-Ethoxy-2-(*o*-tolyl)furan (325i)



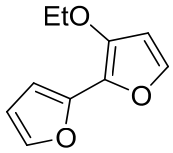
Prepared according to the General Furan Procedure from propargylic alcohol **316i** (500 mg, 2.01 mmol) in EtOH (2.0 M) to give the *furan* **325i** as a colorless oil (177 mg, 0.875 mmol, 44%); R_f = 0.64 (10:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2979s (C-H), 1618s; ^{1}H NMR (400 MHz; MeOH-d$_4$) 7.52–7.48 (1H, m, Ar*H*), 7.41 (1H, d, *J* = 2.0, Ar*H*), 7.24–7.17 (3H, m, Ar*H*), 6.53 (1H, d, *J* = 2.0, Ar*H*), 4.02 (2H, q, *J* = 7.1, OC*H*$_2$), 2.39 (3H, s, ArC*H*$_3$), 1.32 (3H, t, *J* = 7.1, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz; MeOH-d$_4$) 145.1 (*Ar*), 141.7 (*Ar*), 139.2 (*Ar*), 137.0 (*Ar*), 131.6 (*Ar*), 131.3 (*Ar*), 129.5 (*Ar*), 128.4 (*Ar*), 126.4 (*Ar*), 104.9 (*Ar*), 68.2 (O*C*H$_2$), 21.1 (Ar*C*H$_3$), 15.5 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 203.1075; $C_{13}H_{15}O_2$ requires 203.1072.

Methyl 3-(3-ethoxyfuran-2-yl)benzoate (325j)



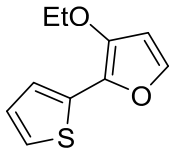
Prepared according to the General Furan Procedure from propargylic alcohol **316j** (500 mg, 1.71 mmol) in EtOH (0.50 M) to give the *furan* **325j** as a pale wax (302 mg, 1.23 mmol, 72%); R_f = 0.47 (10:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2981s (C-H), 1720s (C=O), 1667s, 1431s; ^{1}H NMR (400 MHz; MeOH-d$_4$) 8.43 (1H, t, *J* = 1.4, Ar*H*), 8.00 (1H, dt, *J* = 7.8, 1.4, Ar*H*), 7.80 (1H, dt, *J* = 7.8, 1.4, Ar*H*), 7.47 (1H, t, *J* = 7.8, Ar*H*), 7.43 (1H, d, *J* = 2.1, Ar*H*), 6.61 (1H, d, *J* = 2.1, Ar*H*), 4.17 (2H, q, *J* = 7.0, OC*H*$_2$), 3.94 (3H, s, OC*H*$_3$), 1.46 (3H, t, *J* = 7.0, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz; MeOH-d$_4$) 167.2 (*C*(O)), 145.3 (*Ar*), 140.9 (*Ar*), 135.4 (*Ar*), 131.4 (*Ar*), 130.2 (*Ar*), 128.3 (*Ar*), 126.7 (*Ar*), 125.9 (*Ar*), 123.3 (*Ar*), 103.7 (*Ar*), 66.9 (O*C*H$_2$), 51.2 (O*C*H$_3$), 14.1 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 247.0971; $C_{14}H_{15}O_4$ requires 247.0970.

3-Ethoxy-2,2'-bifuran (325k)



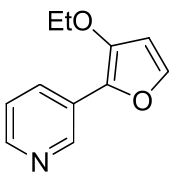
Prepared according to the General Furan Procedure from propargylic alcohol **316k** (500 mg, 2.23 mmol) in EtOH (0.50 M) to give the *furan* **325k** as a colorless oil (102 mg, 0.572 mmol, 26%); R_f = 0.50 (10:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}); 3150m, 2981s (C-H), 1629s, 1575s, 1415s; ^{1}H NMR (400 MHz; MeOH-d$_4$) 7.47 (1H, d, *J* = 2.0, Ar*H*), 7.35 (1H, d, *J* = 2.2, Ar*H*), 6.53 (1H, d, *J* = 2.2, Ar*H*), 6.50 (1H, dd, *J* = 3.4, 2.0, Ar*H*), 6.45 (1H, d, *J* = 3.4, Ar*H*), 4.10 (2H, q, *J* = 6.9, OCH_2), 1.39 (3H, t, *J* = 6.9, CH$_2$CH_3); ^{13}C NMR (100 MHz; MeOH-d$_4$) 145.5 (*Ar*), 143.2 (*Ar*), 140.6 (*Ar*), 140.5 (*Ar*), 112.0 (*Ar*), 110.7 (*Ar*), 103.9 (*Ar*), 103.6 (*Ar*), 67.01 (O*C*H$_2$), 14.0 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 179.070; $C_{10}H_{10}O_3$ requires 179.0708.

3-Ethoxy-2-(thiophen-2-yl)furan (325l)



Prepared according to the General Furan Procedure from propargylic alcohol **316l** (500 mg, 2.23 mmol) in EtOH (0.50 M) to give the *furan* **325l** as a colorless oil (328 mg, 1.69 mmol, 78%); R_f = 0.52 (10:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2980s (C-H), 1620s; ^{1}H NMR (400 MHz; MeOH-d$_4$) 7.32 (1H, d, *J* = 2.2, Ar*H*), 7.27–7.22 (2H, m, Ar*H*), 7.05–7.02 (1H, m, Ar*H*), 6.52 (1H, d, *J* = 2.2, Ar*H*), 4.12 (2H, q, *J* = 7.1, OCH_2), 1.42 (3H, t, *J* = 7.1, CH$_2$CH_3); ^{13}C NMR (100 MHz; MeOH-d$_4$) 142.6 (*Ar*), 139.9 (*Ar*), 134.6 (*Ar*), 132.3 (*Ar*), 126.6 (*Ar*), 122.1 (*Ar*), 120.0 (*Ar*), 103.7 (*Ar*), 67.1 (O*C*H$_2$), 14.1 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 195.0473; $C_{10}H_{11}O_2S$ requires 195.0473.

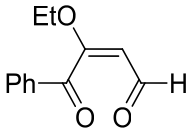
3-(3-Ethoxyfuran-2-yl)pyridine (325m)



Subjecting propargylic alcohol **316m** to the General Furan Procedure in EtOH (0.50 M) resulted in no reaction.

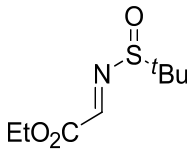
A stirring solution of propargylic alcohol **316m** (200 mg, 0.851 mmol) and MsOH (0.28 mL, 0.48 g, 4.3 mmol) in EtOH (4.2 mL) was treated with $[PPh_3AuNTf_2]_2PhMe$ (33 mg, 0.021 mmol, 2.5 mol%, 5.0 mol% [Au]) at RT. The resulting solution was stirred for 2 h at RT before it was treated with water (5.0 mL) and stirred for a further 1 h. The reaction was then cooled to 0 °C, diluted with Et_2O (20 mL) and quenched with aq. sat. $NaHCO_3$ (20 mL). The aq. extract was washed with Et_2O (3 × 20 mL) and the combined organic extracts were dried (phase separator) and concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (0 to 10% petrol 30–40 °C: TBME) to give the *furan* **325m** as a colorless oil (117 mg, 0.619 mmol, 73%); R_f = 0.23 (10:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2959w (C-H), 1659s, 1678s, 1440s; ^{1}H NMR (400 MHz; MeOH-d_4) 8.94 (1H, d, *J* = 1.7, Ar*H*), 8.31 (1H, dd, *J* = 4.9, 1.7, Ar*H*), 8.14 (1H, d, *J* = 8.1, Ar*H*), 7.49 (1H, d, *J* = 2.2, Ar*H*), 7.44 (1H, dd, *J* = 8.1, 4.9, Ar*H*), 6.64 (1H, d, *J* = 2.2, Ar*H*), 4.19 (2H, q, *J* = 7.0, OCH_2), 1.45 (3H, t, *J* = 7.0, CH_2CH_3); ^{13}C NMR (100 MHz; MeOH-d_4) 146.5 (*Ar*), 145.0 (*Ar*), 142.9 (*Ar*), 142.1 (*Ar*), 132.9 (*Ar*), 129.9 (*Ar*), 127.8 (*Ar*), 123.8 (*Ar*), 103.6 (*Ar*), 67.0 (OCH_2), 14.0 (CH_2CH_3); HRMS (CI^+) found $[M+H]^+$ 190.0863; $C_{11}H_{12}NO_2$ requires 190.0868.

(*E*)-3-Ethoxy-4-oxo-4-phenylbut-2-enal (326)



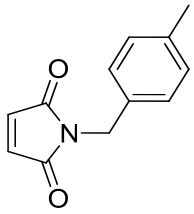
A solution of furan **325e** (103 mg, 0.548 mmol) in PhMe (2.0 mL) was heated at reflux under an atmosphere of air for 24 h. The reaction was then allowed to cool to RT before it was concentrated *in vacuo* to give the crude product. This was purified by flash column chromatography (4:1 petrol 40–60 °C:EtOAc) to give the *aldehyde* **326** as a white crystalline solid (61 mg, 0.30 mmol, 55%); m.p. 52–54 °C; R_f = 0.50 (1:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2981s (C-H), 1757s (C=O), 1675s (C=O), 1630s, 1597s, 1451s; ^{1}H NMR (600 MHz; $CDCl_3$) 9.51 (1H, d, *J* = 7.8, C(O)*H*), 7.93 (2H, d, *J* = 7.6, Ar*H*), 7.66 (1H, t, *J* = 7.6, Ar*H*), 7.52 (2H, t, *J* = 7.6), 5.73 (1H, d, *J* = 7.8, EtOCC*H*), 4.12 (2H, q, *J* = 7.1, OCH_2), 1.44 (3H, t, *J* = 7.1, CH_2CH_3); ^{13}C NMR (150 MHz; $CDCl_3$) 189.8 (*C*(O)H), 189.6 (*C*(O)Ph), 172.0 (EtO*C*), 134.9 (*Ar*), 134.7 (*Ar*), 130.1 (*Ar*), 129.1 (*Ar*), 107.8 (C(O)*C*H), 66.3 (OCH_2), 14.1 (CH_2CH_3); HRMS (CI^+) found $[M+H]^+$ 205.0859; $C_{12}H_{13}O_3$ requires 205.0859.

(*E*)-Ethyl 2-((tert-butylsulfinyl)imino)acetate (328)[192]



According to the modified procedure of Fei *et al.*[192]: 2-Methylpropane-2-sulfinamide (3.00 g, 24.8 mmol) was added to a stirring mixture of ethyl 2-oxoacetate (50% in PhMe, 4.9 mL, 25 mmol) and activated 4 Å molecular sieves (16.0 g) in PhMe (50 mL). The reaction mixture was stirred at 50 °C for 24 h before it was allowed to reach room temperature. The reaction was filtered and the volatile components were removed *in vacuo* to give imine **328** as a yellow oil (3.24 g, 15.8 mmol, 64%); R_f = 0.27 (5:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2982s (C-H), 1744s, 1724s, 1695s, 1606s, 1470s; ^{1}H NMR (400 MHz; $CDCl_3$) 8.01 (1H, s, N=C*H*), 4.39 (2H, q, *J* = 7.1, C*H*$_2$CH$_3$), 1.39 (3H, t, *J* = 7.1, CH$_2$C*H*$_3$), 1.28 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (125 MHz; $CDCl_3$) 161.1 (*C*(O)), 155.6 (*C*=N), 62.4 (*C*H$_2$CH$_3$), 58.9 (*C*(CH$_3$)$_3$), 22.7 (C(*C*H$_3$)$_3$), 14.1 (CH$_2$*C*H$_3$); data in accordance with the literature.[192]

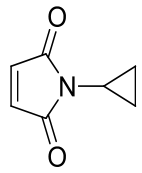
1-(4-Methylbenzyl)-1*H*-pyrrole-2,5-dione (329a)



According to the modified procedure of Ordónez *et al.*[193]: *p*-Tolylmethanamine (2.6 mL, 2.4 g, 20 mmol) was added to a stirring solution of maleic anhydride (2.00 g, 20.4 mmol) in AcOH (40 mL) at RT and the resulting solution was heated at reflux for 3 h. The reaction was then allowed to cool to RT and concentrated *in vacuo* before being redissolved in EtOAc (50 mL) and washed with aq. sat. NH_4Cl. The aq. extract was washed with EtOAc (3 × 50 mL) and the combined organic extracts were dried (phase separator) and concentrated *in vacuo* to give the crude product. This was purified by flash column chromatography (0 to 100% cyclohexane: EtOAc) to give *imide* **329a** as a white crystalline solid (1.23 g, 6.11 mmol, 30%); m.p. = 100–102 °C; R_f = 0.62 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 3097m (C-H), 2941m (C-H), 1696s (C=O), 1515s, 1443s; ^{1}H NMR (400 MHz; MeOH-d$_4$) 7.15–7.10 (4H, m, Ar*H*), 7.06 (2H, s, *H*C=C*H*), 4.55 (2H, s, NC*H*$_2$), 2.27 (3H, s, ArC*H*$_3$); ^{13}C NMR (100 MHz; MeOH-d$_4$) 170.8 (*C*(O)),

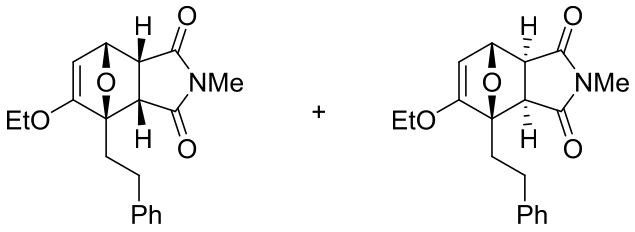
136.6 (*Ar*), 134.6 (*C*H=*C*H), 133.7 (*Ar*), 129.1 (*Ar*), 127.2 (*Ar*), 40.7 (N*C*H$_2$), 20.6 (Ar*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 202.0860; $C_{12}H_{12}NO_2$ requires 200.0868.

1-Cyclopropyl-1*H*-pyrrole-2,5-dione (329b)



According to the modified procedure of Ordónez *et al*.[193]: Cyclopropanamine (1.4 mL, 1.1 g, 20 mmol) was added to a stirring solution of maleic anhydride (2.00 g, 20.4 mmol) in AcOH (40 mL) at RT and the resulting solution was heated at reflux for 2 h. The reaction was then allowed to cool to RT and concentrated *in vacuo* before being dissolved in EtOAc (50 mL) and washed with aq. sat. $NaHCO_3$. The aq. extract was washed with EtOAc (3 × 50 mL) and the combined organic extracts were dried (phase separator) and concentrated *in vacuo* to give the crude product. This was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give *imide* **329b** as a white crystalline solid (1.30 g, 9.48 mmol, 47%); m.p. = 57–59 °C; R_f = 0.55 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2977s (C-H), 1775m, 1757s (C=O), 1400s; ^{1}H NMR (400 MHz; DMSO-d$_6$) 6.93 (2H, s, *H*C=C*H*), 2.52–2.45 (1H, m, NC*H*), 0.85–0.79 (2H, m, CH(C*H*H')$_2$) 0.78–0.72 (2H, m, CH(CH*H*')$_2$); ^{13}C NMR (100 MHz; DMSO-d$_6$) 171.4 (*C*(O)), 134.2 (*C*H=*C*H), 19.7 (N*C*H), 4.4 (NCH(*C*H$_2$)$_2$); HRMS (CI$^+$) found [M+H]$^+$ 138.0555; $C_7H_8NO_2$ requires 138.0555.

(3a*S*,4*R*,7*R*,7a*R*)-5-Ethoxy-2-methyl-4-phenethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (e*ndo*-330a) and (3a*R*,4*R*,7*R*,7a*S*)-5-Ethoxy-2-methyl-4-phenethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (e*xo*-330a)



endo-**330a** *exo*-**330a**

Method A (0.500 mmol): Prepared from furan **225a** (108 mg, 0.500 mmol) and *N*-methylmaleimide according to the General Cycloaddition Procedure to give a mixture of the *cantharimides* **330a** as a colorless oil (153 mg, 0.467 mmol, 93%; *endo*:*exo* = 70:30).

Method A (4.62 mmol): Prepared from furan **225a** (1.00 g, 4.62 mmol) and *N*-methylmaleimide according to the General Cycloaddition Procedure to give the crude product (*endo*:*exo* = 75:25). Purification by flash column chromatography (0 to 100% TBME:cyclohexane) gave the *cantharimide endo*-**330a** (906 mg, 2.77 mmol, 60%). Further elution of the column gave a mixture of the *cantharimide endo*-**330a** and the *cantharimide exo*-**330a** (202 mg, 0.618 mmol, 13%). Further elution of the column gave the *cantharimide exo*-**330a** (310 mg, 0.948 mmol, 21%).

Method B: A solution of *N*-methylmaleimide (67 mg, 0.60 mmol) and furan **225a** (108 mg, 0.500 mmol) in DMC (0.50 mL) was stirred at 80 °C for 16 h. The reaction was then allowed to cool to RT before it was diluted with EtOAc and loaded onto an aminopropyl cartridge. After 5 minutes the cartridge was then washed with EtOAc and the filtrate was concentrated *in vacuo* to give a mixture of the *cantharimides* **330a** as a colorless oil (153 mg, 0.467 mmol, 93%; *endo*:*exo* = 55:45).

Method C: A solution of $[PPh_3AuNTf_2]_2PhMe$ (60 mg, 1.0 mol%, 2.0 mol% [Au]) in EtOH (1.9 mL) was added dropwise to a stirring solution of propargylic alcohol **325a** (1.00 g, 3.81 mmol) in EtOH (1.9 mL) at RT. The resulting solution was stirred for 3 h before it was treated with PPh_3 (25 mg, 2.5 mol%). After a further 1 h the reaction was treated with *N*-methylmaleimide (508 mg, 4.57 mmol) and stirred for 16 h at RT. The reaction mixture was then loaded onto an aminopropyl cartridge and, after 5 minutes,

eluted with EtOAc. The filtrate was concentrated *in vacuo* to give the crude product (*endo*:*exo* = 70:30), which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give a mixture of the *cantharimides* **330a** as a colorless oil (828 mg, 2.53 mmol, 66%; *endo*:*exo* = 70:30).

***Cantharimide* e*ndo*-330a**: Isolated a white crystalline solid. m.p. 90–92 °C; R_f = 0.62 (2:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2981s (C-H), 1774m (C=O), 1710s (C=O), 1623s, 1432s; ^{1}H NMR (600 MHz; $CDCl_3$) 7.29 (2H, t, *J* = 7.3, Ar*H*), 7.23 (2H, d, *J* = 7.3, Ar*H*), 7.19 (1H, t, *J* = 7.3, Ar*H*), 5.18 (1H, dd, *J* = 5.3, 1.4, COC*H*), 4.96 (1H, d, *J* = 1.4, C=C*H*), 3.85–3.80 (1H, m, OC*H*H'), 3.67 (1H, dd, *J* = 7.6, 5.3, OCHC*H*CH), 3.57–3.51 (1H, m, OCH*H*'), 3.19 (1H, d, *J* = 7.6, OCHCHC*H*), 2.83–2.79 (5H, m, NCH_3; PhCH_2), 2.62–2.55 (1H, m, PhCH$_2$C*H*H'), 2.28–2.22 (1H, m, PhCH$_2$CH*H*'), 1.27 (3H, t, *J* = 7.0, CH$_2$CH_3); ^{13}C NMR (150 MHz; $CDCl_3$) 175.7 (*C*(O)), 174.2 (*C*(O)), 164.1 (EtO*C*), 141.7 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 126.1 (*Ar*), 96.6 (C=*C*H), 89.6 (*C*OCH), 78.2 (COC*H*), 66.9 (O*C*H$_2$), 51.4 (OCH*C*HCH), 49.8 (OCHCH*C*H), 31.9 (PhCH$_2$*C*H$_2$), 30.5 (Ph*C*H$_2$), 24.5 (N*C*H$_3$), 14.2 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 328.1544; $C_{19}H_{22}NO_4$ requires 328.1543.

***Cantharimide* e*xo*-330a**: Isolated as a pale wax. R_f = 0.50 (1:1 cyclohexane:EtOAc); ^{1}H NMR (400 MHz; MeOH-d$_4$) 7.36–7.16 (5H, m, Ar*H*), 5.20 (1H, d, *J* = 2.0, C=C*H*), 5.13 (1H, d, *J* = 2.0, COC*H*), 3.94–3.76 (2H, m, OCH_2), 3.15 (1H, d, *J* = 6.4, C*H*C(O)), 2.95 (1H, d, *J* = 6.4, C*H*C(O)), 2.90–2.74 (2H, m, PhCH_2), 2.44–2.36 (1H, m, PhCH$_2$C*H*H'), 2.31–2.22 (1H, m, PhCH$_2$CH*H*'), 1.39 (3H, t, *J* = 7.1, CH$_2$CH_3); ^{13}C NMR (150 MHz; MeOH-d$_4$) 177.1 (*C*(O)), 175.6 (*C*(O)), 166.6 (*C*OEt), 142.1 (*Ar*), 128.0 (*Ar*), 127.9 (*Ar*), 125.5 (*Ar*), 99.5 (C=*C*H), 88.8 (*C*OCH), 79.9 (CO*C*H), 66.5 (O*C*H$_2$), 54.3 (*C*HC(O)), 49.1 (*C*HC(O)), 30.4 (*C*H$_2$), 29.7 (*C*H$_2$), 23.4 (N*C*H$_3$), 13.2 (CH$_2$*C*H$_3$).

(3a*S*,4*R*,7*R*,7a*R*)-5-Methoxy-2-methyl-4-phenethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*endo*-320) and (3a*R*,4*R*,7*R*,7a*S*)-5-Methoxy-2-methyl-4-phenethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*exo*-320)[190]

endo-**320** *exo*-**320**

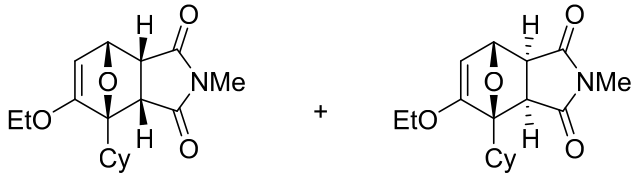
Prepared from furan **318** (101 mg, 0.500 mmol) and *N*-methylmaleimide according to the General Cycloaddition Procedure over 4 h to give the crude product (*endo*:*exo* = 80:20). This was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give the cantharimide *endo*-**320** as a white crystalline solid (105 mg, 0.335 mmol, 67%). Further elution of the column gave the cantharimide *exo*-**320** as a white crystalline solid (34 mg, 0.11 mmol, 22%).

Cantharimide e*ndo*-320: m.p. 94–96 °C; R_f = 0.40 (1:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2931s (C-H), 1774s, 1699s (C=O), 1625s, 1433s; ^{1}H NMR (600 MHz; $CDCl_3$) 7.27 (2H, t, *J* = 7.5, Ar*H*), 7.24 (2H, d, *J* = 7.5, Ar*H*), 7.19 (1H, t, *J* = 7.5, Ar*H*), 5.20 (1H, dd, *J* = 5.2, 1.3, COC*H*), 5.02 (1H, d, *J* = 1.3, C=C*H*), 3.70 (1H, dd, *J* = 7.5, 5.2, OCHC*H*CH), 3.53 (3H, s, OCH_3), 3.21 (1H, d, *J* = 7.5, OCHCHC*H*), 2.85 (3H, s, NCH_3), 2.83–2.78 (2H, m, PhCH_2), 2.62–2.56 (1H, m, PhCH$_2$C*H*H'), 2.28–2.22 (1H, m, PhCH$_2$CH*H*'); ^{13}C NMR (150 MHz; $CDCl_3$) 175.6 (*C*(O)), 174.3 (*C*(O)), 165.4 (MeO*C*), 141.6 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 126.1 (*Ar*), 96.9 (C=*C*H), 89.7 (*C*OCH), 78.2 (CO*C*H), 58.2 (O*C*H$_3$), 51.3 (OCH*C*HCH), 49.8 (OCHCH*C*H), 31.9 (PhCH$_2$*C*H$_2$), 30.5 (Ph*C*H$_2$), 24.6 (N*C*H$_3$); data in accordance with the literature.[190]

Cantharimide e*xo*-320: m.p. 149–151 °C; R_f = 0.50 (1:2 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2922s (C-H), 1764s, 1698s (C=O), 1633s, 1440s; ^{1}H NMR (600 MHz; $CDCl_3$) 7.29–7.25 (2H, m, Ar*H*), 7.24–7.21 (2H, m, Ar*H*), 7.17 (1H, t, *J* = 7.2, Ar*H*), 5.18 (1H, s, C=C*H*), 5.16 (1H, s, COC*H*), 3.66 (3H, s, OCH_3), 3.14 (1H, d, *J* = 6.4, C*H*C(O)), 2.96 (3H, s, N*C*H$_3$), 2.93 (1H, d, *J* = 6.4, C*H*C(O)), 2.85–2.73 (2H, m, PhCH_2), 2.39–2.33 (1H, m, PhCH$_2$C*H*H'), 2.30–2.20 (1H, m, PhCH$_2$CH*H*'); ^{13}C NMR (150 MHz; $CDCl_3$)

176.4 (*C*(O)), 174.9 (*C*(O)), 168.4 (MeO*C*), 141.9 (*Ar*), 128.5 (*Ar*), 128.4 (*Ar*), 126.0 (*Ar*), 99.6 (C=*C*H), 89500 M.3 (*C*OCH), 79.9 (CO*C*H), 58.3 (O*C*H$_3$), 54.4 (*C*HC(O)), 49.2 (*C*HC(O)), 30.8 (Ph*C*H$_2$), 25.0 (PhCH$_2$*C*H$_2$), 25.0 (N*C*H$_3$); data in accordance with the literature. [190]

(3a*S*,4*R*,7*R*,7a*R*)-4-Cyclohexyl-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (e*ndo*-330b) and (3a*R*,4*R*,7*R*,7a*S*)-4-Cyclohexyl-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (e*xo*-330b)

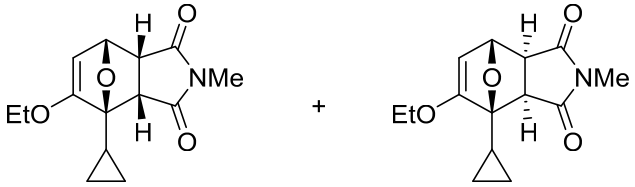


endo-**330b** *exo*-**330b**

Prepared from furan **325b** (97 mg, 0.50 mmol) and *N*-methylmaleimide according to the General Cycloaddition Procedure over 4 h to give a mixture of the *cantharimides* **330b** as a colorless oil (145 mg, 0.475 mmol, 95%, *endo*:*exo* = 85:15); R_f = 0.51 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2983s (C-H), 1773m, 1702s (C=O), 1624s, 1433s; ^{1}H NMR (400 MHz; MeOH-d$_4$) 5.21 (1H, dd, *J* = 2.1, 1.0, C=C*H exo*-**330b**), 5.06 (1H, dd, *J* = 5.0, 2.1, COC*H endo*-**330b**), 5.00 (1H, d, *J* = 2.1, C=C*H endo*-**330b**), 4.96 (1H, d, *J* = 2.1, COC*H exo*-**330b**), 3.88–3.75 (1H, m, OC*H*H' *endo*-**330b**; 2H, m, OC*H*$_2$ *exo*-**330b**), 3.63 (1H, dd, *J* = 7.4, 5.0, OCHC*H*CH *endo*-**330b**), 3.58–3.51 (1H, m, OCH*H*' *endo*-**330b**), 3.51 (1H, d, *J* = 7.4, CyCC*H endo*-**330b**), 3.18–3.13 (2H, m, 2 × C*H*C(O) *exo*-**330b**), 2.91 (3H, s, NC*H*$_3$ *exo*-**330b**), 2.79 (3H, s, NC*H*$_3$ *endo*-**330b**), 2.36–2.29 (1H, m, C*H*H' *exo*-**330b**), 2.14–1.91 (3H, m, 3 × C*H*H' *endo*-**330b**), 1.91–1.66 (4H, m, 4 × C*H*H' *endo*-**330b**), 1.44–1.14 (3H, m, CH$_2$C*H*$_3$ *endo*-**330b**; 3H, m, CH$_2$C*H*$_3$ *exo*-**330b**; 3H, 3 × C*H*H' *endo*-**330b**) [9 × C*H*H' protons of *exo*-**330b** cannot be assigned with confidence]; ^{13}C NMR (100 MHz; MeOH-d$_4$) 177.1 (*C*(O)), 176.3 (*C*(O)), 175.3 (*C*(O)), 175.1 (*C*(O)), 167.4 (*C*OEt), 164.3 (*C*OEt), 100.6 (C=*C*H *exo*-**330b**), 96.6 (C=*C*H *endo*-**330b**), 92.3 (Cy*C*), 91.8 (Cy*C*), 79.3 (CO*C*H *exo*-**330b**), 77.3 (CO*C*H *endo*-**330b**), 66.4 (O*C*H$_2$), 66.2 (O*C*H$_2$), 54.3 (C*H*C(O) *exo*-**330b**), 51.3 (OCHC*H*CH *endo*-**330b**), 47.9 (C*H*C(O) *exo*-**330b**), 46.2 (CyCC*H endo*-**330b**), 39.2 (C*H*(CH$_2$)$_2$ *exo*-**330b**), 37.0 (C*H*(CH$_2$)$_2$ *endo*-**330b**), 27.8 (*C*H$_2$), 27.5 (*C*H$_2$), 26.7 (*C*H$_2$), 26.4 (*C*H$_2$), 26.3 (*C*H$_2$), 26.3 (*C*H$_2$), 26.2 (*C*H$_2$), 26.1 (*C*H$_2$), 26.1 (*C*H$_2$), 26.0 (*C*H$_2$), 23.5 (NCH$_3$), 23.2 (N*C*H$_3$), 13.3

(CH_2CH_3), 13.2 (CH_2CH_3); HRMS (CI^+) found $[M+H]^+$ 306.1700; $C_{17}H_{24}NO_4$ requires 306.1705.

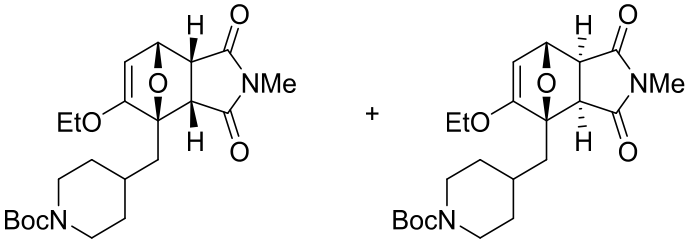
(3a*S*,4*R*,7*R*,7a*R*)-4-Cyclopropyl-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (e*ndo*-330c) and (3a*R*,4*R*,7*R*,7a*S*)-4-Cyclopropyl-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (e*xo*-330c)



endo-**330c** *exo*-**330c**

Prepared from furan **325c** (76 mg, 0.50 mmol) and *N*-methylmaleimide according to the General Cycloaddition Procedure over 4 h to give a mixture of the *cantharimides* **330c** as a colorless oil (118 mg, 0.448 mmol, 90%, *endo*:*exo* = 80:20); R_f = 0.48 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2980s (C-H), 1702s (C=O), 1624m; ^{1}H NMR (400 MHz; MeOH-d_4) 5.15 (1H, d, *J* = 2.0, C=C*H exo*-**330c**), 5.04 (1H, dd, *J* = 5.1, 2.0, COC*H endo*-**330c**), 5.00 (1H, d, *J* = 2.0, C=C*H endo*-**330c**), 4.96 (1H, d, *J* = 2.0, COC*H exo*-**330c**), 3.93–3.76 (1H, m, OC*H*H' *endo*-**330c**; 2H, m, OCH_2 *exo*-**330c**), 3.67 (1H, dd, *J* = 7.6, 5.1, OCHC*H*CH *endo*-**330c**), 3.62–3.54 (1H, m, OCH*H*' *endo*-**330c**), 3.24–3.20 (1H, d, *J* = 7.6, OCHCHC*H endo*-**330c**; 1H, m, C*H*C(O) *exo*-**330c**), 3.00 (1H, d, *J* = 6.4, C*H*C(O) *exo*-**330c**), 2.92 (3H, s, NCH_3 *exo*-**330c**), 2.81 (3H, s, NCH_3 *endo*-**330c**), 1.57–1.47 (1H, m, C*H*(CH_2)$_2$ *endo*-**330c**), 1.44–1.38 (1H, m, C*H*(CH_2)$_2$ *exo*-**330c**), 1.34 (3H, t, *J* = 7.0, CH_2CH_3 *exo*-**330c**), 1.26 (3H, t, *J* = 7.1, CH_2CH_3 *endo*-**330c**), 0.79–0.49 (4H, m, CH(CH_2)$_2$ *endo*-**330c**, 3H, m, CH(CH_2)(C*H*H') *exo*-**330c**), 0.34–0.30 (1H, m, CH(CH_2)(CH*H*') *exo*-**330c**); ^{13}C NMR (100 MHz; MeOH-d_4) 177.2 (*C*(O)), 176.2 (*C*(O)), 175.6 (*C*(O)), 174.9 (*C*(O)), 167.5 (*C*OEt), 164.7 (*C*OEt), 98.6 (C=*C*H *exo*-**330c**), 95.9 (C=*C*H *endo*-**330c**), 89.1 (^{c}Pr*C*), 88.4 (^{c}Pr*C*), 79.1 (CO*C*H *exo*-**330c**), 77.3 (CO*C*H *endo*-**330c**), 66.4 (O*C*H_2), 66.4 (O*C*H_2), 54.6 (*C*HC(O) *exo*-**330c**), 51.2 (OCH*C*HCH *endo*-**330c**), 49.5 (*C*HC(O) *exo*-**330c**), 48.8 (OCHCH*C*H *endo*-**330c**), 23.4 (N*C*H_3), 23.3 (N*C*H_3), 13.2 (CH_2CH_3), 13.1 (CH_2CH_3), 9.5 (*C*H(CH_2)$_2$), 7.9 (*C*H(CH_2)$_2$), 0.9 (CH(*C*H_2)$_2$), 0.5 (CH(*C*H_2)$_2$), 0.3 (CH(*C*H_2)$_2$); HRMS (CI^+) found $[M+H]^+$ 264.1239; $C_{14}H_{18}NO_4$ requires 264.1236.

tert-Butyl 4-(((3a*S*,4*R*,7*R*,7a*R*)-5-ethoxy-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-epoxyisoindol-4-yl)methyl)piperidine-1-carboxylate (e*ndo*-330d) and _tert_-Butyl 4-(((3a*R*,4*R*,7*R*,7a*S*)-5-ethoxy-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-epoxyisoindol-4-yl)methyl)piperidine-1-carboxylate (e*xo*-330d)

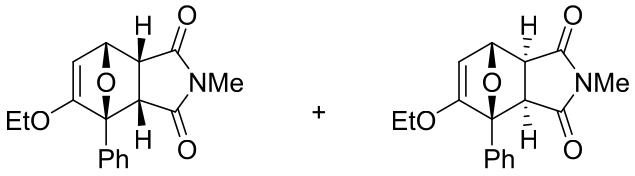


endo-**330d** *exo*-**330d**

Prepared from furan **325d** (44 mg, 0.14 mmol) and *N*-methylmaleimide according to the General Cycloaddition Procedure over 4 h to give a mixture of the *cantharimides* **330d** as a colorless oil (51 mg, 0.12 mmol, 85%, *endo*:*exo* = 75:25); R_f = 0.50 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2929s (C-H), 1701s (C=O), 1428m; ^{1}H NMR (600 MHz; $CDCl_3$) 5.19–5.16 (1H, m, COC*H* *endo*-**330d**; 1H, m, COC*H* *exo*-**330d**), 5.05 (1H, s, C=C*H* *exo*-**330d**), 4.94 (1H, s, C=C*H* *endo*-**330d**), 4.04 (2H, br. s, NC*H*H' *endo*-**330d**; 2H, br. s, NC*H*H' *exo*-**330d**), 3.89–3.75 (1H, m, OC*H*H' *endo*-**330d**; 2H, m, OCH_2 *exo*-**330d**), 3.64 (1H, dd, *J* = 7.7, *J* = 5.0, OCHC*H*CH *endo*-**330d**), 3.58–3.52 (1H, m, OCH*H*' *endo*-**330d**), 3.17 (1H, d, *J* = 7.7, OCHCHC*H* *endo*-**330d**), 3.08 (1H, d, *J* = 6.2, C*H*C(O) *exo*-**330d**), 2.98 (3H, s, NCH_3, *exo*-**330d**), 2.84 (3H, s, NCH_3 *endo*-**330d**), 2.83 (1H, d, *J* = 6.2, C*H*C(O) *exo*-**330d**), 2.76–2.63 (2H, m, NCH*H*' *endo*-**330d**; 2H, br. s, NCH*H*' *exo*-**330d**), 2.30 (1H, dd, *J* = 15.0, 5.5, COCC*H*H' *endo*-**330d**), 2.09 (1H, dd, *J* = 15.4, 5.5, CHOCC*H*H' *exo*-**330d**), 1.91–1.65 (1H, m, COCCH*H*' *endo*-**330d**; 2H, m, N(CH_2C*H*H')$_2$ *endo*-**330d**; 1H, m, N(CH_2CH_2)$_2$C*H* *endo*-**330d**; 2H, m, COCCH*H*' *exo*-**330d**; 2H, m, N(CH_2C*H*H')$_2$ *exo*-**330d**; 1H, m, N(CH_2CH_2)$_2$C*H* *exo*-**330d**), 1.59 (9H, s, C(CH_3)$_3$ *exo*-**330d**), 1.46 (9H, s, C(CH_3)$_3$ *endo*-**330d**), 1.35 (3H, t, *J* = 7.0, CH_2CH_3 *exo*-**330d**), 1.28 (3H, t, *J* = 7.0, CH_2CH_3 *endo*-**330d**), 1.25–1.11 (1H, m, N(CH_2C*H*H')$_2$ *endo*-**330d**; 2H, m, N(CH_2CH*H*')$_2$ *exo*-**330d**); ^{13}C NMR (150 MHz; $CDCl_3$) 176.4 (*C*(O)N), 175.5 (*C*(O)N), 175.0 (*C*(O)N), 174.1 (*C*(O)N), 166.9 (EtO*C*), 164.1 (EtO*C*), 154.9 (*C*O^{t}Bu), 98.8 (C=*C*H *exo*-**330d**), 96.1 (C=*C*H *endo*-**330d**), 89.6 (*C*OCH), 89.2 (*C*OCH), 79.9 (CO*C*H), 79.2 (*C*Me$_3$), 79.1 (*C*Me$_3$), 78.1 (CO*C*H), 66.8 (OCH_2), 66.6 (OCH_2), 54.2 (*C*H), 51.0 (*C*H), 50.8 (*C*H), 49.8 (*C*H), 43.9 (br. N*C*H$_2$ *endo*-**330d**; N*C*H$_2$ *exo*-**330d**), 36.1 (*C*H$_2$), 33.1 (br. NCH$_2$*C*H$_2$), 32.9 (N(CH_2CH_2)$_2$*C*H), 32.6 (N(CH_2CH_2)$_2$*C*H), 32.5

(br. NCH_2CH_2), 28.5 ($C(CH_3)_3$ *endo*-**330d**; $C(CH_3)_3$ *exo*-**330d**) 24.8 (NCH_3), 24.4 (NCH_3), 14.2 (CH_2CH_3), 14.1 (CH_2CH_3); HRMS (CI^+) found $[M+H]^+$ 421.2333; $C_{22}H_{33}N_2O_6$ requires 421.2339; Strong ROE between OCHC*H*CH *endo*-**330d** and COC*H* *endo*-**330d**; Weak ROE between OCHC*H*CH *exo*-**330d** and COC*H* *exo*-**330d**.

(3a*S*,4*S*,7*R*,7a*R*)-5-Ethoxy-2-methyl-4-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (e*ndo*-330e) and (3a*R*,4*S*,7*R*,7a*S*)-5-Ethoxy-2-methyl-4-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (e*xo*-330e)



endo-**330e** *exo*-**330e**

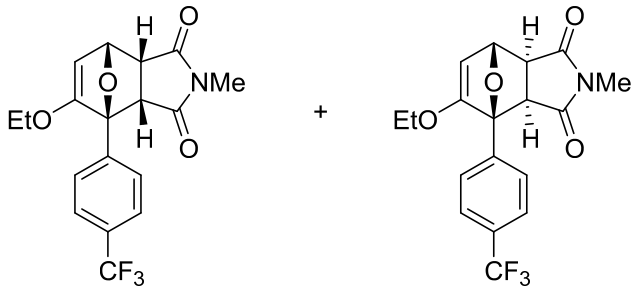
Experiment A (0.428 mmol scale): Prepared from furan **325e** (94 mg, 0.50 mmol) and *N*-methylmaleimide according to the General Cycloaddition Procedure over 6 h to give a mixture of the *cantharimides* **330e** as a white crystalline solid (128 mg, 0.428 mmol, 86%, *endo*:*exo* = 80:20).

Experiment B (5.32 mmol scale): Prepared from furan **325e** (1.00 g, 5.32 mmol) and *N*-methylmaleimide according to the General Cycloaddition Procedure over 24 h to give the crude product, which was purified by flash column chromatography (0 to 70% TBME:cyclohexane) to give *cantharimide endo*-**330e** as a white crystalline solid (1.04 g, 3.47 mmol, 65%). Further elution of the column gave the *cantharimide exo*-**330e** as a white crystalline solid (334 mg, 1.12 mmol, 21%).

Cantharimide e*ndo*-330e: m.p. 96–98 °C; R_f = 0.45 (3:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2982 (C-H), 1774s, 1700s (C=O), 1623s, 1500s, 1432s; ^1H NMR (600 MHz; $CDCl_3$) 7.89–7.79 (2H, m, Ar*H*), 7.47–7.38 (3H, m, Ar*H*), 5.32 (1H, dd, *J* = 5.2, 2.1, COC*H*), 5.02 (1H, d, *J* = 2.1, C=C*H*), 3.84–3.78 (2H, m, OC*H*H'; OCHC*H*CH), 3.58–3.52 (2H, m, OCH*H*'; PhCC*H*), 2.91 (3H, s, NCH_3), 1.18 (3H, t, *J* = 7.1, CH_2CH_3); ^{13}C NMR (150 MHz; $CDCl_3$) 175.4 (*C*(O)), 174.3 (*C*(O)), 164.9 (*C*OEt), 134.7 (*Ar*), 128.7 (*Ar*), 128.4 (*Ar*), 127.2 (*Ar*), 95.5 (C=*C*H), 90.3 (*C*Ph), 77.9 (CO*C*H), 67.1 (OCH_2), 51.8 (OCH*C*HCH), 51.0 (PhC*C*H), 24.6 (NCH_3), 13.9 (CH_2CH_3); HRMS (CI^+) found $[M+H]^+$ 300.1239; $C_{17}H_{18}NO_4$ requires 300.1230.

Cantharimide e*xo*-330e: m.p. 119–121 °C; R_f = 0.38 (3:1 petrol 40–60 °C:EtOAc); ^{1}H NMR (400 MHz; MeOH-d$_4$) 7.51–7.45 (2H, m, Ar*H*), 7.39–7.29 (3H, m, Ar*H*), 5.28 (1H, d, *J* = 2.2, C=C*H*), 5.22 (1H, d, *J* = 2.2, COC*H*), 3.83 (2H, q, *J* = 7.1, OCH_2), 3.46 (1H, d, *J* = 6.4, C*H*C(O)), 3.38–3.34 (1H, m, C*H*C(O)), 2.80 (3H, s, NCH_3), 1.28 (3H, t, *J* = 7.1, CH_2CH_3); ^{13}C NMR (400 MHz; MeOH-d$_4$) 177.0 (*C*(O)), 174.5 (*C*(O)), 167.1 (*C*OEt), 132.6 (*Ar*), 127.5 (*Ar*), 127.1 (*Ar*), 126.4 (*Ar*), 98.1 (C=*C*H), 90.2 (*C*Ph), 79.8 (CO*C*H), 66.6 (OCH_2), 54.6 (*C*HC(O)), 49.9 (*C*HC(O)), 23.3 (NCH_3), 13.0 (CH_2CH_3).

(3a*S*,4*S*,7*R*,7a*R*)-5-Ethoxy-2-methyl-4-(4-(trifluoromethyl)phenyl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (e*ndo*-330f) and (3a*R*,4*S*,7*R*,7a*S*)-5-Ethoxy-2-methyl-4-(4-(trifluoromethyl)phenyl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (e*xo*-330f)

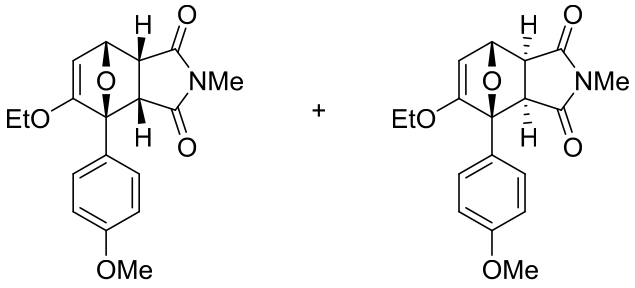


endo-**330f** *exo*-**330f**

Prepared from furan **325f** (64 mg, 0.25 mmol) and *N*-methylmaleimide according to the General Cycloaddition Procedure over 24 h to give a mixture of the *cantharimides* **330f** as a white crystalline solid (69 mg, 0.18 mmol, 75%, *endo*:*exo* = 80:20); m.p. = 243–245 °C; R_f = 0.55 and 0.75 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2986m (C-H), 1776m, 1702s (C=O), 1625s; ^{1}H NMR (400 MHz; MeOH-d$_4$) 7.98 (2H, d, *J* = 7.7, Ar*H* *endo*-**330f**), 7.71 (2H, d, *J* = 7.7, Ar*H* *endo*-**330f**), 7.66–7.65 (4H, m, Ar*H* *exo*-**330f**), 5.31–5.30 (1H, dd, *J* = 5.1, 2.2, COC*H* *endo*-**330f**; 1H, m, COC*H* *exo*-**330f**), 5.24 (1H, d, *J* = 2.2, C=C*H* *exo*-**330f**), 5.14 (1H, d, *J* = 2.2, C=C*H* *endo*-**330f**), 3.87 (1H, dd, *J* = 5.1, 7.6, OCHC*H*CH *endo*-**330f**), 3.86–3.77 (1H, m, OC*H*H' *endo*-**330f**; 2H, m, OCH_2 *exo*-**330f**), 3.60 (1H, d, *J* = 7.6, OCHCHC*H* *endo*-**330f**), 3.60–3.55 (1H, m, OCH*H*' *endo*-**330f**), 3.51 (1H, d, *J* = 6.4, C*H*C(O) *exo*-**330f**), 3.36 (1H, d, *J* = 6.4, C*H*C(O) *exo*-**330f**), 2.87 (3H, s, NCH_3 *endo*-**330f**), 2.78 (3H, s, NCH_3 *exo*-**330f**), 1.26 (3H, t, *J* = 7.1, CH_2CH_3 *exo*-**330f**), 1.15 (3H, t, *J* = 7.1, CH_2CH_3 *endo*-**330f**); ^{13}C NMR (150 MHz; MeOH-d$_4$) 176.7 (*C*(O)), 175.6 (*C*(O)), 174.5 (*C*(O)), 174.3 (*C*(O)), 166.4 (*C*OEt), 164.3 (*C*OEt), 139.6 (*Ar*), 137.1 (*Ar*), 130.1 (q, $J_{C\text{-}F}$ = 33.2, *Ar*), 129.9 (q, $J_{C\text{-}F}$ = 32.4, Ar), 127.7 (*Ar*),

127.2 (*Ar*), 124.4 (q, $J_{C\text{-}F}$ = 4.4, *Ar*), 124.0 (q, $J_{C\text{-}F}$ = 4.4, *Ar*), 124.4 (q, $J_{C\text{-}F}$ = 270.9, CF_3), 124.3 (q, $J_{C\text{-}F}$ = 270.9, CF_3), 98.4 (C=C*H exo*-**330f**), 95.6 (C=C*H endo*-**330f**), 89.6 (*C*OCH), 89.3 (*C*OCH), 80.1 (CO*C*H *exo*-**330f**), 77.9 (CO*C*H *endo*-**330f**), 66.9 (OCH_2), 66.9 (OCH_2), 54.4 (*C*HC(O) *exo*-**330f**), 51.5 (OCH*C*HCH *endo*-**330f**), 50.8 (OCHCH*C*H *endo*-**330f**), 49.9 (*C*HC(O) *exo*-**330f**), 23.4 (NCH_3), 23.3 (NCH_3), 13.0 (CH_2CH_3), 12.9 (CH_2CH_3); HRMS (CI^+) found $[M+H]^+$ 368.1111; $C_{18}H_{17}F_3NO_4$ requires 368.1110.

(3a*S*,4*S*,7*R*,7a*R*)-5-Ethoxy-4-(4-methoxyphenyl)-2-methyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (e*ndo*-330g) and (3a*R*,4*S*,7*R*,7a*S*)-5-Ethoxy-4-(4-methoxyphenyl)-2-Methyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (e*xo*-330g)

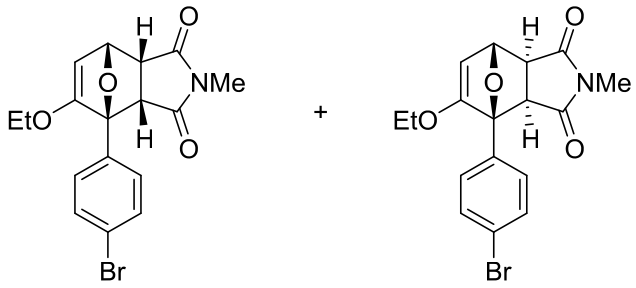


endo-**330g** *exo*-**330g**

Prepared from furan **325g** (55 mg, 0.25 mmol) and *N*-methylmaleimide according to the General Cycloaddition Procedure over 4 h to give a mixture of the *cantharimides* **330g** as a colorless oil (74 mg, 0.23 mmol, 90%, *endo*:*exo* = 80:20); R_f = 0.15 and 0.08 (3:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2981s (C-H), 1773m, 1702s (C=O), 1622s, 1519s; ^{1}H NMR (400 MHz; $CDCl_3$) 7.76–7.71 (2H, m, Ar*H endo*-**330g**), 7.46–7.43 (2H, m, Ar*H exo*-**330g**), 7.01–6.94 (2H, m, Ar*H endo*-**330g**; 2H, m, Ar*H exo*-**330g**), 5.33–5.30 (1H, dd, *J* = 2.0, 5.1, COC*H endo*-**330g**; 1H, m, COC*H exo*-**330g**), 5.15 (1H, d, *J* = 2.2, C=C*H exo*-**330g**), 5.04 (1H, d, *J* = 2.0, C=C*H endo*-**330g**), 3.87–3.76 (3H, m, OCH_3 *endo*-**330g**, 1H, m, OCHC*H*CH *endo*-**330g**; 1H, m, OC*H*H' *endo*-**330g**; 3H, m, OCH_3 *exo*-**330g**; 1H, m, OCH_2 *exo*-**330g**), 3.60–3.52 (1H, m, OCHCHC*H endo*-**330g**; OCH*H*' *endo*-**330g**), 3.30 (1H, d, *J* = 6.3, C(O)C*H exo*-**330g**), 2.26 (1H, d, *J* = 6.3, C(O)C*H exo*-**330g**), 2.92 (3H, m, NCH_3 *endo*-**330g**), 2.88 (3H, m, NCH_3 *exo*-**330g**), 1.30 (3H, t, *J* = 7.1, CH_2CH_3 *exo*-**330g**), 1.20 (3H, t, *J* = 7.1, CH_2CH_3 *endo*-**330g**); ^{13}C NMR (100 MHz; $CDCl_3$) 176.2 (*C*(O)), 175.3 (*C*(O)), 174.2 (*C*(O)), 173.9 (*C*(O)), 167.5 (EtO*C*), 164.9 (EtO*C*), 159.8 (*Ar*), 159.3 (*Ar*), 128.5 (*Ar*), 127.7 (*Ar*), 126.8 (*Ar*), 124.1 (*Ar*), 113.7 (*Ar*), 113.2 (*Ar*), 97.9 (C=C*H exo*-**330g**), 95.4 (C=C*H endo*-**330g**), 90.2 (*C*OCH), 90.1 (*C*OCH), 79.8

(CO*C*H *exo*-**330g**), 77.7 (CO*C*H *endo*-**330g**), 66.9 (O*C*H$_2$ *endo*-**330g**; O*C*H$_2$ *exo*-**330g**), 55.3 (O*C*H$_3$), 55.1 (O*C*H$_3$), 54.7 (C*H*), 51.8 (C*H*), 50.9 (*C*H), 50.0 (*C*H), 24.8 (N*C*H$_3$), 24.6 (N*C*H$_3$), 14.8 (CH$_2$*C*H$_3$), 13.8 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 330.1347; $C_{18}H_{20}NO_5$ requires 330.1342.

(3a*S*,4*S*,7*R*,7a*R*)-4-(4-Bromophenyl)-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*endo*-330h) and (3a*R*,4*S*,7*R*,7a*S*)-4-(4-Bromophenyl)-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*exo*-330h)



endo-**330h** *exo*-**330h**

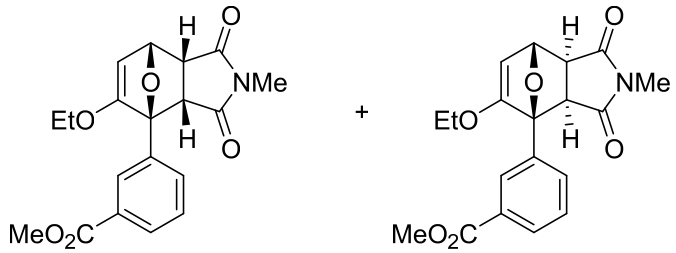
Prepared from furan **325h** (134 mg, 0.500 mmol) and *N*-methylmaleimide according to the General Cycloaddition Procedure over 24 to give the crude product (*endo*:*exo* = 80:20), which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give a mixture of the *cantharimides* **330h** as a colorless oil (149 mg, 0.392 mmol, 78%, *endo*:*exo* = 20:1); R_f = 0.28 and 0.49 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2981s (C-H), 1775w, 1702s (C=O), 1624s, 1491s; ^{1}H NMR (400 MHz; MeOH-d$_4$, *endo*-**330h**) 7.75–7.61 (2H, m, Ar*H*), 7.61–7.55 (2H, m, Ar*H*), 5.29 (1H, dd, *J* = 5.1, 2.1, COC*H*), 5.13 (1H, d, *J* = 2.1, C=C*H*), 3.87 (1H, dd, *J* = 5.1, 7.8, OCHC*H*CH), 3.84–3.77 (1H, m, OC*H*H'), 3.60 (1H, d, *J* = 7.8, OCHCHC*H*), 3.60–3.53 (1H, m, OCH*H*'), 2.88 (3H, s, NC*H*$_3$), 1.17 (3H, t, *J* = 7.1, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz; MeOH-d$_4$, *endo*-**330h**), 175.7 (*C*(O)), 174.6 (*C*(O)), 164.4 (*C*OEt), 134.5 (*Ar*), 130.7 (*Ar*), 129.0 (*Ar*), 122.1 (*Ar*), 95.5 (C=*C*H), 89.4 (*C*OCH), 77.7 (CO*C*H), 66.8 (O*C*H$_2$), 51.5 (*C*HC(O)), 50.7 (*C*HC(O)), 23.4 (N*C*H$_3$), 12.9 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 378.0340; $C_{17}H_{17}{}^{79}BrNO_4$ requires 378.0341.

(3a*S*,4*S*,7*R*,7a*R*)-4-(*o*-Tolyl)-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*endo*-330i) and (3a*R*,4*S*,7*R*,7a*S*)-4-(*o*-Tolyl)-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*exo*-330i)

endo-**330i** *exo*-**330i**

Prepared from furan **325i** (101 mg, 0.500 mmol) and *N*-methylmaleimide according to the General Cycloaddition Procedure over 24 h to give a mixture of the *cantharimides* **330i** as a colorless oil (135 mg, 0.431 mmol, 86%, *endo*:*exo* = 80:20); R_f = 0.63 and 0.59 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2981s (C-H), 1773m, 1700s (C=O), 1625s, 1433s; ^{1}H NMR (400 MHz; DMSO-d$_6$) 8.01–7.97 (1H, m, Ar*H endo*-**330i**), 7.36–7.28 (2H, m, Ar*H endo*-**330i**; 1H, m, Ar*H exo*-**330i**), 7.23–7.17 (1H, m, Ar*H endo*-**330i**; 2H, m, Ar*H exo*-**330i**), 7.13–7.08 (1H, m, Ar*H exo*-**330i**), 5.36 (1H, d, *J* = 2.2, C=C*H exo*-**330i**), 5.31 (1H, dd, *J* = 5.1, 2.0, COC*H endo*-**330i**), 5.19–5.16 (1H, m, C=C*H endo*-**330i**; 1H, m, COC*H exo*-**330i**). 4.07 (1H, d, *J* = 7.8, OCHCHC*H endo*-**330i**), 3.83–3.73 (1H, m, OC*H*H' *endo*-**330i**; 1H, m, OCHC*H*CH *endo*-**330i**; 1H, m, OCH_2 *exo*-**330i**; 1H, m, C*H*C(O) *exo*-**330i**), 3.60–3.52 (1H, m, OCH*H*' *endo*-**330i**), 3.34–3.31 (1H, m, C*H*C(O) *exo*-**330i**; *H*OD), 2.76 (3H, s, NCH_3 *endo*-**330i**), 2.69 (3H, s, NCH_3 *exo*-**330i**), 2.59 (3H, s, ArCH_3 *exo*-**330i**), 2.31 (3H, s, ArCH_3 *endo*-**330i**), 1.16 (3H, t, *J* = 7.0, CH_2CH_3 *exo*-**330i**), 1.02 (3H, t, *J* = 7.0, CH_2CH_3 *endo*-**330i**); ^{13}C NMR (100 MHz; $CDCl_3$) 176.7 (*C*(O)), 175.5 (*C*(O)), 174.5 (*C*(O)), 174.3 (*C*(O)), 166.9 (*C*OEt), 164.3 (*C*OEt), 139.3 *(Ar)*, 137.3 *(Ar)*, 132.4 *(Ar)*, 132.4 *(Ar)*, 131.4 *(Ar)*, 131.2 *(Ar)*, 130.4 *(Ar)*, 129.4 *(Ar)*, 128.2 *(Ar)*, 125.9 *(Ar)*, 125.5 *(Ar)*, 100.0 (C=*C*H *exo*-**330i**), 96.0 (C=*C*H *endo*-**330i**), 91.3 (*C*OCH), 90.8 (*C*OCH), 78.8 (CO*C*H *exo*-**330i**), 77.9 (CO*C*H *endo*-**330i**), 67.0 (OCH_2), 66.8 (OCH_2), 53.7 (C*H*C(O) *exo*-**330i**), 51.0 (OCH*C*HCH *endo*-**330i**), 49.3 (C*H*C(O) *exo*-**330i**), 49.0 (OCHCH*C*H *endo*-**330i**), 24.7 (N*C*H$_3$), 24.7 (N*C*H$_3$), 22.3 (Ar*C*H$_3$), 20.8 (Ar*C*H$_3$), 14.4 (CH_2CH_3), 14.2 (CH_2CH_3); HRMS (CI$^+$) found [M+H]$^+$ 314.1399; $C_{18}H_{20}NO_4$ requires 314.1392.

Methyl 3-((3a*S*,4*S*,7*R*,7a*R*)-5-ethoxy-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-epoxyisoindol-4-yl)benzoate (*endo*-330j) and Methyl 3-((3a*R*,4*S*,7*R*,7a*S*)-5-ethoxy-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-epoxyisoindol-4-yl)benzoate (*exo*-330j)



endo-**330j** *exo*-**330j**

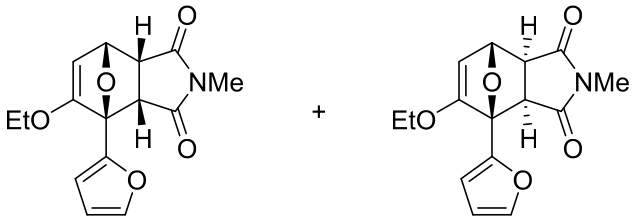
Prepared from furan **325j** (123 mg, 0.500 mmol) and *N*-methylmaleimide according to the General Cycloaddition Procedure over 24 h to give the crude product (*endo*:*exo* = 75:25). This was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give the *cantharimide endo*-**330j** (107 mg, 0.300 mmol, 60%). Further elution of the column gave the *cantharimide exo*-**330j** (41 mg, 0.12 mmol, 23%).

***Cantharimide* endo-330j**: Isolated as a white crystalline solid; m.p. = 126–128 °C; R_f = 0.44 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2980s (C-H), 1775m, 1720s (C=O ester and imide), 1624s, 1433s; ^{1}H NMR (400 MHz; DMSO-d$_6$) 8.30 (1H, t, *J* = 1.6, Ar*H*), 8.06–7.96 (2H, m, Ar*H*), 7.63 (1H, t, *J* = 7.7, Ar*H*), 5.36 (1H, dd, *J* = 5.1, 2.0, COC*H*), 5.22 (1H, d, *J* = 2.0, C=C*H*), 3.92–3.85 (4H, m, CO_2CH_3; OCHC*H*CH), 3.83–3.74 (1H, m, OC*H*H'), 3.68 (1H, d, *J* = 7.6, OCHCHC*H*), 3.59–3.50 (1H, m, OCH*H*'), 2.78 (3H, s, NCH_3), 1.05 (3H, t, *J* = 7.0, CH_2CH_3); ^{13}C NMR (100 MHz; DMSO-d$_6$) 175.3 (*C*(O)N), 174.5 (*C*(O)N), 166.5 (*C*(O)OMe or *C*OEt), 164.0 (*C*(O)OMe or *C*OEt), 136.4 (*Ar*), 132.5 (*Ar*), 130.0 (*Ar*), 129.6 (*Ar*), 129.2 (*Ar*), 128.2 (*Ar*), 97.0 (C=*C*H), 89.3 (*C*OCH), 77.7 (CO*C*H), 67.1 (OCH_2), 52.7 (OCH_3 or OCH*C*HCH), 51.7 (OCH_3 or OCH*C*HCH), 50.9 (OCHCH*C*H), 24.8 (NCH_3), 14.1 (CH_2CH_3); HRMS (CI$^+$) found [M+H]$^+$ 358.1294; $C_{19}H_{20}NO_6$ requires 358.1291.

***Cantharimide* exo-330j**: Isolated as a white crystalline solid; m.p. = 118–120 °C; R_f = 0.27 (1:1 cyclohexane:EtOAc); ^{1}H NMR (400 MHz; DMSO-d$_6$) 7.99 (1H, t, *J* = 1.4, Ar*H*), 7.93 (1H, dd, *J* = 7.7, 1.4, Ar*H*), 7.75–7.69 (1H, m, Ar*H*), 7.58–7.52 (1H, m, Ar*H*), 5.37 (1H, d, *J* = 2.2, C=C*H*), 5.24 (1H, d, *J* = 2.2, COC*H*), 3.87 (3H, s, OCH_3), 3.80 (2H, q, *J* = 7.0, OCH_2), 3.56 (1H, d, *J* = 6.4, C*H*C(O)), 3.37 (1H, d, *J* = 6.4, C*H*C(O)), 2.69

(3H, s, NC*H*$_3$), 1.18 (3H, t, *J* = 7.0, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz; DMSO-d$_6$) 176.4 (*C*(O)N), 174.2 (*C*(O)N), 166.6 (*C*(O)OMe or *C*OEt), 165.9 (*C*(O)OMe or *C*OEt), 133.9 (*Ar*), 132.2 (*Ar*), 129.5 (*Ar*), 129.1 (*Ar*), 128.5 (*Ar*), 127.4 (*Ar*), 99.7 (C=*C*H), 89.7 (*C*OCH), 80.0 (CO*C*H), 67.1 (O*C*H$_2$), 54.5 (*C*HC(O)), 52.7 (O*C*H$_3$), 50.0 (*C*HC(O)), 24.7 (N*C*H$_3$), 14.3 (CH$_2$*C*H$_3$).

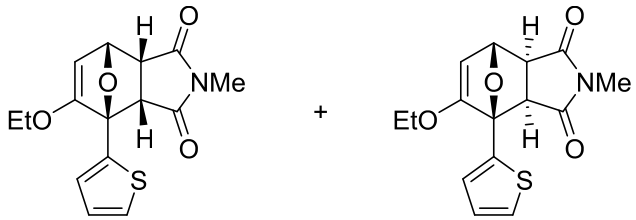
(3a*S*,4*S*,7*R*,7a*R*)-4-(Furan-2-yl)-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*endo*-330k) and (3a*R*,4*S*,7*R*,7a*S*)-4-(Furan-2-yl)-5-ethoxy-2-methyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*exo*-330k)



endo-**330k** *exo*-**330k**

Prepared from furan **325k** (104 mg, 0.584 mmol) and *N*-methylmaleimide according to the General Cycloaddition Procedure over 24 h to give the crude product (*endo*:*exo* = 90:10). This was purified by flash column chromatography (0 to 100% EtOAc:cyclohexane) to give the a mixture of the *cantharimides* **330k** as a white crystalline solid (143 mg, 0.494 mmol, 85%, *endo*:*exo* = 95:5); m.p. = 122–124 °C; R_f = 0.16 (2:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2982s (C-H), 1775m, 1701s (C=O), 1631s 1434s; ^{1}H NMR (400 MHz; DMSO-d$_6$, *endo*-**330k**) 7.83–7.73 (1H, m, Ar*H*), 6.84 (1H, d, *J* = 3.4, Ar*H*), 6.57 (1H, dd, *J* = 3.4, 2.0, Ar*H*), 5.31–5.21 (2H, m, C=C*H*; COC*H*), 3.92 (1H, d, *J* = 7.6, OCHCHC*H*), 3.88–3.81 (2H, m, OC*H*H'; OCHC*H*CH), 3.59–3.51 (1H, m, OCH*H*'), 2.72 (3H, s, NCH$_3$), 1.10 (3H, t, *J* = 7.1, CH$_2$C*H*$_3$); ^{1}H NMR (400 MHz; DMSO-d$_6$, *exo*-**330k**) 7.72–7.71 (1H, m, Ar*H*), 6.70 (1H, d, *J* = 3.2, Ar*H*), 6.46 (1H, dd, *J* = 2.0, 3.4, Ar*H*), 5.36 (1H, d, *J* = 2.0, C=C*H* or COC*H*), 5.16 (1H, d, *J* = 2.0, C=C*H* or COC*H*), 2.78 (3H, s, NC*H*$_3$), 1.21 (3H, t, *J* = 6.9, CH$_2$C*H*$_3$), remaining resonances obscured by the major diastereoisomer; ^{13}C NMR (100 MHz; DMSO-d$_6$, *endo*-**330k**), 175.4 (*C*(O)), 173.6 (*C*(O)), 162.5 (*C*OEt), 147.6 (*Ar*), 144.9 (*Ar*), 112.8 (*Ar*), 111.2 (*Ar*), 97.9 (C=*C*H), 84.4 (*C*OCH), 76.0 (CO*C*H), 67.2 (O*C*H$_2$), 51.0 (*C*HC(O)), 48.9 (*C*HC(O)), 24.6 (N*C*H$_3$)), 14.3 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 290.1028; $C_{15}H_{16}NO_5$ requires 290.1029.

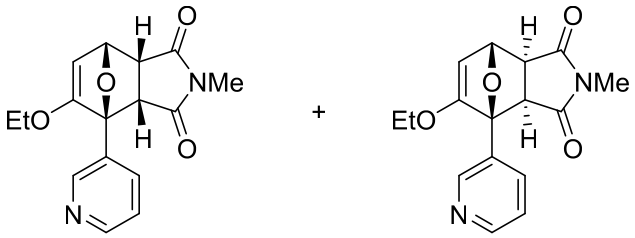
(3a*S*,4*R*,7*R*,7a*R*)-5-Ethoxy-2-methyl-4-(thiophen-2-yl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*endo*-330l) and (3a*R*,4*R*,7*R*,7a*S*)-5-Ethoxy-2-methyl-4-(thiophen-2-yl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*exo*-330l)



endo-**330l** *exo*-**330l**

Prepared from furan **325l** (97 mg, 0.50 mmol) and *N*-methylmaleimide according to the General Cycloaddition Procedure over 24 h to give a mixture of the *cantharimides* **330l** as a colorless oil (147 mg, 0.481 mmol, 96%, *endo*: *exo* = 70:30); R_f = 0.42 and 0.63 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2982s (C-H), 1774m, 1700s (C=O), 1626s, 1433s; ^{1}H NMR (400 MHz; DMSO-d$_6$) 7.63 (1H, dd, *J* = 5.0, 1.1, Ar*H endo*-**330l**), 7.57–7.48 (1H, m, Ar*H endo*-**330l**; 1H, m, Ar*H exo*-**330l**), 7.25 (1H, dd, *J* = 3.5, 1.1, Ar*H exo*-**330l**), 7.14 (1H, dd, *J* = 5.0, 3.7, Ar*H endo*-**330l**), 7.07 (1H, dd, *J* = 5.1, 3.5, Ar*H exo*-**330l**), 5.34 (1H, d, *J* = 2.0, C=C*H exo*-**330l**), 5.27 (2H, dd, *J* = 5.1, 2.2, COC*H endo*-**330l**), 5.21 (1H, d, *J* = 2.2, C=C*H endo*-**330l**), 5.18 (1H, d, *J* = 2.0, COC*H exo*-**330l**), 3.90–3.77 (1H, m, OCHC*H*CH *endo*-**330l**; 1H, m, OC*H*H' *endo*-**330l**; 1H, m, OCH_2 *exo*-**330l**), 3.74 (1H, d, *J* = 7.8, OCHCHC*H endo*-**330l**), 3.59–3.51 (1H, m, OCH*H*' *endo*-**330l**), 3.37 (1H, d, *J* = 6.6, C*H*C(O) *exo*-**330l**), 3.33–3.32 (1H, m, C*H*C(O) *exo*-**330l**; *H*OD), 2.75 (3H, s, NCH_3 *endo*-**330l**; 3H, s, NCH_3 *exo*-**330l**), 1.22 (3H, t, *J* = 7.1, CH_2CH_3 *exo*-**330l**), 1.09 (3H, t, *J* = 7.0, CH_2CH_3 *endo*-**330l**); ^{13}C NMR (100 MHz; DMSO-d$_6$) 176.3 (*C*(O)), 175.4 (*C*(O)), 173.9 (*C*(O)), 173.7 (*C*(O)), 165.7 (EtO*C*), 163.4 (EtO*C*), 137.2 (*Ar*), 134.5 (*Ar*), 128.4 (*Ar*), 127.7 (*Ar*), 127.4 (*Ar*), 127.2 (*Ar*), 127.0 (*Ar*), 126.4 (*Ar*), 99.4 (C=*C*H *exo*-**330l**), 97.2 (C=*C*H *endo*-**330l**), 88.2 (*C*OCH), 87.2 (*C*OCH), 80.2 (CO*C*H *exo*-**330l**), 77.9 (CO*C*H *endo*-**330l**), 67.2 (OCH_2), 67.2 (OCH_2), 55.0 (*C*H), 51.7 (*C*H), 51.6 (*C*H), 51.0 (*C*H), 24.8 (NCH_3), 24.7 (NCH_3), 14.4 (CH_2CH_3), 14.2 (CH_2CH_3); HRMS (CI$^+$) found [M+H]$^+$ 306.0795; $C_{15}H_{16}NO_4S$ requires 306.0800.

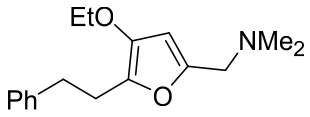
(3a*S*,4*S*,7*R*,7a*R*)-5-Ethoxy-2-methyl-4-(pyridin-3-yl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*endo*-330m) and (3a*R*,4*S*,7*R*,7a*S*)-5-Ethoxy-2-methyl-4-(pyridin-3-yl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*exo*-330m)



endo-**330m** *exo*-**330m**

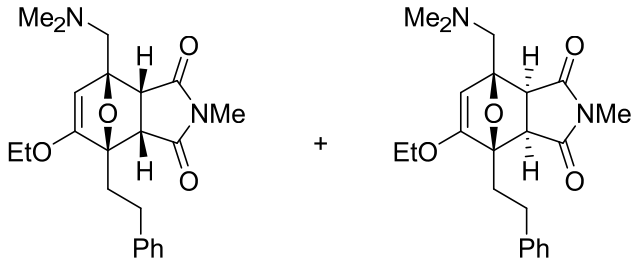
Prepared from furan **325m** (25 mg, 0.015 mmol) and *N*-methylmaleimide according to the General Cycloaddition Procedure over 24 h to give a mixture of the *cantharimides* **330m** as a colorless oil (37 mg, 0.12 mmol, 92%, *endo*: *exo* = 70:30); R_f = 0.28 and 0.16 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2980s (C-H), 1774s, 1695s (C=O), 1623s, 1480s; ^{1}H NMR (400 MHz; DMSO-d$_6$) 8.93 (1H, m, Ar*H endo*-**330m**), 8.66 (1H, m, Ar*H exo*-**330m**), 8.58 (1H, d, *J* = 5.0, Ar*H endo*-**330m**), 8.52 (1H, d, *J* = 5.0, ArH *exo*-**330m**), 8.26 (1H, d, *J* = 8.2, Ar*H endo*-**330m**), 7.95 (1H, d, *J* = 8.3, Ar*H exo*-**330m**), 7.52 (1H, dd, *J* = 8.2, 5.0, Ar*H endo*-**330m**), 7.47 (1H, dd, *J* = 8.3, 5.0, Ar*H exo*-**330m**), 5.36–5.35 (1H, m, COC*H endo*-**330m**; 1H, m, C=C*H exo*-**330m**), 5.29 (1H, d, *J* = 2.0, COC*H exo*-**330m**), 5.19 (1H, d, *J* = 2.2, C=C*H endo*-**330m**), 3.92–3.79 (1H, m, OCHC*H*CH *endo*-**330m**; 1H, m, OC*H*H' *endo*-**330m**; 2H, m, OCH_2 *exo*-**330m**), 3.67 (1H, d, *J* = 7.6, OCHCHC*H endo*-**330m**), 3.64–3.56 (1H, m, OCH*H*' *endo*-**330m**; 1H, m, C*H*C(O) *exo*-**330m**), 3.39 (1H, d, *J* = 6.4, C*H*C(O) *exo*-**330m**), 2.89 (3H, s, NCH_3 *endo*-**330m**), 2.81 (3H, s, NCH_3 *endo*-**330m**), 1.28 (3H, t, *J* = 7.1, CH_2CH_3 *exo*-**330m**), 1.18 (3H, t, *J* = 7.1, CH_2CH_3 *endo*-**330m**); ^{13}C NMR (100 MHz; MeOH-d$_4$) 176.6 (*C*(O)), 175.5 (*C*(O)), 174.4 (*C*(O)), 174.3 (*C*(O)), 166.2 (*C*OEt), 163.9 (*C*OEt), 148.6 (*Ar*), 148.0 (*Ar*), 147.5 (*Ar*), 147.0 (*Ar*), 135.8 (*Ar*), 135.3 (*Ar*), 132.0 (*Ar*), 129.7 (*Ar*), 123.3 (*Ar*), 123.0 (*Ar*), 98.5 (C=*C*H *exo*-**330m**), 95.8 (C=*C*H *endo*-**330m**), 88.3 (*C*OCH), 87.9 (*C*OCH), 80.4 (CO*C*H *exo*-**330m**), 78.2 (CO*C*H *endo*-**330m**), 67.0 (O*C*H_2), 67.0 (O*C*H_2), 54.3 (C*H*C(O) *exo*-**330m**), 51.3 (OCH*C*HCH *endo*-**330m**), 50.8 (OCHCH*C*H *endo*-**330m**), 49.7 (CO*C*H *exo*-**330m**), 23.4 (N*C*H_3), 23.4 (N*C*H_3), 13.0 (CH_2*C*H_3), 12.9 (CH_2*C*H_3); HRMS (CI$^+$) found [M+H]$^+$ 301.1189; $C_{16}H_{17}N_2O_4$ requires 301.1188.

1-(4-Ethoxy-5-phenethylfuran-2-yl)-*N*,*N*-dimethylmethanamine (332)



Prepared according to the modified procedure of Sheppard *et al.*[190]: A stirring solution of furan **325a** (50 mg, 0.23 mmol) in MeCN (2.3 mL) was treated with dimethylmethylideneammonium iodide (85 mg, 0.46 mmol) and the resulting mixture was stirred at RT for 16 h before it was concentrated *in vacuo* to give the crude product. This was purified by flash column chromatography (1:1 petrol 40–60 °C: Et_2O with 1% NEt_3) to give the *furan* **332** as a colorless oil (49 mg, 0.18 mmol, 78%); R_f = 0.30 (1:1 petrol 40–60 °C: EtOAc); ν_{max} (film/cm^{-1}) 2927s (C-H), 1635s, 1495s, 1453s, 1420s; ^{1}H NMR (600 MHz; MeOH-d$_4$) 7.22–7.18 (2H, m, Ar*H*), 7.14–7.10 (3H, m, Ar*H*), 6.19 (1H, s, Ar*H*), 3.71 (2H, q, *J* = 7.1, OC*H*$_2$), 3.39 (2H, s, C*H*$_2$N), 2.90–2.82 (4H, m, C*H*$_2$C*H*$_2$Ph), 2.22 (6H, s, N(C*H*$_3$)$_2$), 1.17 (3H, t, *J* = 7.1, CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz; MeOH-d$_4$) 148.6 (*Ar*), 144.1 (*Ar*), 142.7 (*Ar*), 140.6 (*Ar*), 129.5 (*Ar*), 129.2 (*Ar*), 126.9 (*Ar*), 104.8 (*Ar*), 68.7 (O*C*H$_2$), 56.6 (N*C*H$_2$), 44.7 (N(*C*H$_3$)$_2$), 35.3 (*C*H$_2$), 28.0 (*C*H$_2$), 15.4 (*C*H$_3$);. HRMS (ESI$^+$) found [M+H]$^+$ 274.1818; $C_{17}H_{24}NO_2$ requires 274.1807.

(3a*S*,4*R*,7*R*,7a*R*)-5-Ethoxy-2-methyl-4-phenethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*endo*-333) and (3a*R*,4*R*,7*R*,7a*S*)-5-Ethoxy-2-methyl-4-phenethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*exo*-333)



endo-**333** *exo*-**333**

Prepared from furan **332** (88 mg, 0.32 mmol) and *N*-methylmaleimide according to the General Cycloaddition Procedure over 24 to give a mixture of the *cantharimides* **333** as a colorless oil (116 mg, 0.302 mmol, 94%; *endo*:*exo* = 20:80); R_f = 0.35 (Et_2O); ν_{max} (film/cm^{-1}) 2938s (C-H), 1772m, 1698s (C=O), 1626s, 1454s; ^{1}H NMR (600 MHz; MeOH-d$_4$) 7.29–7.12 (5H, m, Ar*H* *endo*-**333**; 5H, m, Ar*H* *exo*-**333**), 5.28 (1H, s, C=C*H* *exo*-**333**), 5.01 (1H, s, C=C*H* *endo*-**333**), 3.97–3.91 (1H, m, OC*H*H' *exo*-**333**), 3.88–3.82 (1H, m, OC*H*H' *endo*-**333**; 1H, m, OCH*H*' *exo*-**333**), 3.59–3.51 (1H, m, OCH*H*' *endo*-

333), 3.47 (1H, d, *J* = 7.5, $Me_2NCH_2CCHC(O)$ *endo*-**333**), 3.37 (1H, d, *J* = 14.7, Me_2NCHH' *exo*-**333**), 3.33 (1H, d, *J* = 7.5, $EtOCCCHC(O)$ *endo*-**333**), 3.22 (1H, d, *J* = 14.3, Me_2NCHH' *endo*-**333**), 3.15 (1H, d, *J* = 6.4, $Me_2NCH_2CCHC(O)$ *exo*-**333**), 3.02 (1H, d, *J* = 6.4, $EtOCCCHC(O)$ *exo*-**333**), 2.89 (3H, s, $C(O)NCH_3$ *exo*-**333**), 2.82–2.68 (3H, m, $C(O)NCH_3$ *endo*-**333**; 2H, m, CH_2CH_2 *endo*-**333**; 3H, m, $C(O)NCH_3$ *endo*-**333**; 2H, m, CH_2CH_2 *exo*-**333**), 2.74 (1H, d, *J* = 14.3, Me_2NCHH' *endo*-**333**), 2.55 (1H, d, *J* = 14.7, Me_2NCHH' *exo*-**333**), 2.48–2.43 (1H, m, CH_2CHH' *endo*-**333**), 2.34 (6H, s, $N(CH_3)_2$ *endo*-**333**; 6H, s, $N(CH_3)_2$ *exo*-**333**), 2.33–2.06 (1H, m, CH_2CHH' *endo*-**333**; 1H, m, CH_2CH_2 *exo*-**333**), 1.37 (3H, t, *J* = 7.1, CH_2CH_3 *exo*-**333**), 1.25 (3H, t, *J* = 7.1, CH_2CH_3 *endo*-**333**); ^{13}C NMR (150 MHz; MeOH-d_4) 177.4 (*C*(O)), 176.6 (*C*(O)), 176.5 (*C*(O)), 176.3 (*C*(O)), 167.3 (*C*OEt), 165.0 (*C*OEt), 143.4 (*Ar*), 143.1 (*Ar*), 129.5 (*Ar*), 129.4 (*Ar*), 129.3 (*Ar*), 127.0 (*Ar*), 127.0 (*Ar*), 102.6 (C=*C*H *exo*-**333**), 99.1 (C=*C*H *endo*-**333**), 91.2 (*C*OC), 90.9 (*C*OC), 90.8 (*C*OC), 90.2 (*C*OC), 68.0 (OCH_2 *endo*-**333**), 67.9 (OCH_2 *exo*-**333**), 61.7 (NCH_2 *endo*-**333**), 60.3 (NCH_2 *exo*-**333**), 57.7 ($Me_2NCH_2CCHC(O)$ *exo*-**333**), 54.6 ($Me_2NCH_2CCHC(O)$ *endo*-**333**), 52.7 ($EtOCCCHC(O)$ *endo*-**333**), 52.6 ($EtOCCCHC(O)$ *exo*-**333**), 47.3 ($N(CH_3)_2$ *endo*-**333**), 47.2 ($N(CH_3)_2$ *exo*-**333**), 33.2 (CH_2CH_2 *endo*-**333**), 32.1 (CH_2CH_2 *exo*-**333**), 31.6 (CH_2CH_2 *endo*-**333**), 31.1 (CH_2CH_2 *exo*-**333**), 24.9 (NCH_3 imide *exo*-**333**), 24.7 (NCH_3 imide *endo*-**333**), 14.7 (CH_2CH_3 *exo*-**333**), 14.6 (CH_2CH_3 *endo*-**333**); Significant NOE between $Me_2NCH_2CCHC(O)$ and Me_2NCH_2 for *endo*-**333**; No Significant NOE between $Me_2NCH_2CCHC(O)$ and Me_2NCH_2 for *exo*-**333**; HRMS (CI^+) found $[M+H]^+$ 385.2127; $C_{22}H_{29}N_2O_4$ requires 385.2127.

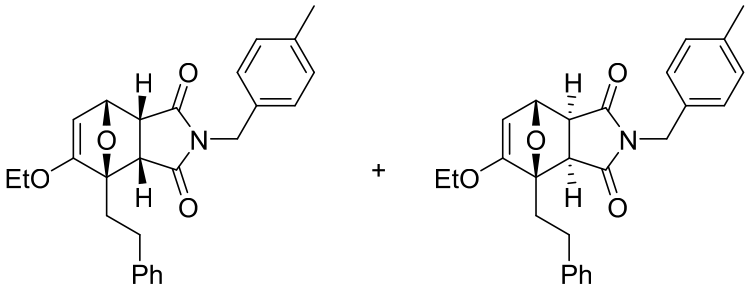
(3a*S*,4*R*,7*R*,7a*R*)-5-Ethoxy-2-phenyl-4-phenethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*endo*-334a) and (3a*R*,4*R*,7*R*,7a*S*)-5-Ethoxy-2-phenyl-4-phenethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*exo*-334a)

endo-**334a** *exo*-**334a**

Prepared from furan **325a** (108 mg, 0.500 mmmol) and 1-phenyl-1*H*-pyrrole-2,5-dione according to the General Cycloaddition Procedure over 4 h to give a mixture of the

cantharimides **334a** as a pale wax (183 mg, 0.470 mmol, 94%, *endo*:*exo* = 65:35); R_f = 0.64 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2977s (C-H), 1713s (C=O), 1624s, 1498s; ^{1}H NMR (400 MHz; $CDCl_3$) 7.51–7.17 (10H, m, Ar*H*, *endo*-**334a**; 10H, m, Ar*H*, *exo*-**334a**), 5.32 (1H, t, *J* = 2.0, COC*H endo*-**334a**), 5.31 (1H, d, *J* = 2.0, COC*H exo*-**334a**), 5.19 (1H, d, *J* = 2.0, C=C*H exo*-**334a**), 5.15 (1H, d, *J* = 2.0, C=C*H endo*-**334a**), 3.96–3.80 (1H, m, OCHC*H*CH *endo*-**334a**; 1H, m, OC*H*H' *endo*-**334a**; 2H, m, OCH_2 *exo*-**334a**), 3.76–3.68 (1H, m, OCH*H*' *endo*-**334a**), 3.38 (1H, d, *J* = 7.8, OCHCHC*H endo*-**334a**), 3.32 (1H, d, *J* = 6.6, C(O)C*H exo*-**334a**), 3.10 (1H, d, *J* = 6.6, C(O)C*H exo*-**334a**), 2.95–2.82 (2H, m, PhCH_2 *endo*-**334a**; 2H, m, PhCH_2 *exo*-**334a**), 2.73–2.63 (1H, m, PhCH_2C*H*H' *endo*-**334a**), 2.50–2.42 (1H, m, PhCH_2C*H*H' *exo*-**334a**), 2.41–2.28 (1H, m, PhCH_2CH*H*' *endo*-**334a**; 1H, m, PhCH_2CH*H*' *exo*-**334a**), 1.40 (3H, t, *J* = 7.1, CH_2CH_3 *exo*-**334a**), 1.33 (3H, t, *J* = 7.1, CH_2CH_3 *endo*-**334a**); ^{13}C NMR (100 MHz; $CDCl_3$) 175.3 (*C*(O)), 174.3 (*C*(O)), 173.8 (*C*(O)), 172.8 (*C*(O)), 167.2 (*C*OEt), 164.4 (*C*OEt), 142.0 (*Ar*), 141.6 (*Ar*), 131.8 (*Ar*), 131.7 (*Ar*), 129.1 (*Ar*), 129.1 (*Ar*), 128.7 (*Ar*), 128.4 (*Ar*), 128.4 (*Ar*), 128.3 (*Ar*), 126.6 (*Ar*), 126.0 (*Ar*), 125.9 (*Ar*), 125.8 (*Ar*), 99.6 (C=C*H exo*-**334a**), 97.0 (C=C*H endo*-**334a**), 90.0 (*C*OCH), 89.7 (*C*OCH), 80.5 (CO*C*H), 78.5 (CO*C*H), 66.9 (O*C*H_2), 66.8 (O*C*H_2), 54.3 (*C*HC(O) *exo*-**334a**), 51.2 (OCH*C*HCH *endo*-**334a**), 49.5 (OCHCH*C*H *endo*-**334a**), 49.2 (*C*HC(O) *exo*-**334a**), 31.9 (*C*H_2), 30.7 (*C*H_2), 30.4 (*C*H_2), 29.5 (*C*H_2), 14.3 (CH_2*C*H_3), 14.3 (CH_2*C*H_3); HRMS (CI^+) found $[M+H]^+$ 390.1708; $C_{24}H_{24}NO_4$ requires 390.1705.

(3a*S*,4*R*,7*R*,7a*R*)-5-Ethoxy-2-(4-methylbenzyl)-4-phenethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*endo*-334b) and (3a*R*,4*R*,7*R*,7a*S*)-5-Ethoxy-2-(4-methylbenzyl)-4-phenethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*exo*-334b)

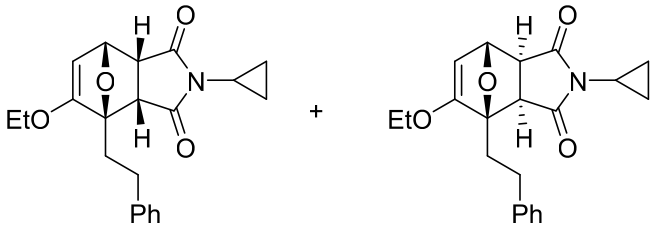


endo-**334b** *exo*-**334b**

Prepared from furan **325a** (108 mg, 0.500 mmol) and imide **329a** according to the General Cycloaddition Procedure over 4 h to give a mixture of the *cantharimides* **334b** as a pale wax (173 mg, 0.414 mmol, 83%, *endo*:*exo* = 55:45); R_f = 0.51 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2977s (C-H), 1771m, 1701s (C=O), 1623m, 1513m, 1430m; ^{1}H NMR (600 MHz; $CDCl_3$) 7.32–7.11 (9H, m, Ar*H endo*-**334b**; 9H, m, Ar*H exo*-**334b**), 5.22 (1H, d, *J* = 1.8, COC*H exo*-**334b**), 5.18 (1H, dd, *J* = 5.1, 1.5, COC*H endo*-**334b**), 5.12 (1H, d, *J* = 1.8, C=C*H exo*-**334b**), 4.75 (1H, d, *J* = 1.5, C=C*H endo*-**334b**), 4.62 (2H, AB system, *J* = 14.7, NCH_2 *exo*-**334b**), 4.53 (1H, d, *J* = 14.0, NC*H*H' *endo*-**334b**), 4.39 (1H, d, *J* = 14.0, NCH*H*' *endo*-**334b**), 3.91–3.89 (1H, m, OC*H*H' *exo*-**334b**), 3.83–3.78 (1H, m, OCH*H*' *exo*-**334b**), 3.69 (1H, dd, *J* = 7.7, 5.1, OCHC*H*CH *endo*-**334b**), 3.33–3.28 (1H, m, OC*H*H' *endo*-**334b**), 3.21 (1H, d, *J* = 7.7, OCHCHC*H endo*-**334b**), 3.14 (1H, d, *J* = 6.4, C(O)C*H exo*-**334b**), 2.92 (1H, d, *J* = 6.4, C(O)C*H exo*-**334b**), 2.86–2.75 (2H, m, CH_2Ph *endo*-**334b**; 2H, m, CH_2Ph *exo*-**334b**), 2.58–2.51 (1H, m, C*H*H*'*CH_2Ph *endo*-**334b**), 2.51–2.46 (1H, m, OCH*H*' *endo*-**334b**), 2.40–2.32 (1H, m, C*H*H*'*CH_2Ph *exo*-**334b**; 3H, m, ArCH_3 *endo*-**334b**; 3H, m, ArCH_3 *endo*-**334b**), 2.17–2.09 (1H, m, CH*H'*CH_2Ph *endo*-**334b**; 1H, m, CH*H'*CH_2Ph *exo*-**334b**), 1.38 (3H, t, *J* = 7.0, *exo*-**334b** CH_2CH_3), 1.06 (3H, t, *J* = 7.0, CH_2CH_3 *endo*-**334b**); ^{13}C NMR (150 MHz; $CDCl_3$) 175.8 (*C*(O)), 175.0 (*C*(O)), 174.5 (*C*(O)), 173.6 (*C*(O)), 167.1 (*C*OEt), 164.2 (*C*OEt), 142.0 (*Ar*), 141.6 (*Ar*), 137.7 (*Ar*), 137.4 (*Ar*), 133.1 (*Ar*), 132.7 (*Ar*), 129.6 (*Ar*), 129.2 (*Ar*), 129.2 (*Ar*), 128.4 (*Ar*), 128.4 (*Ar*), 128.3 (*Ar*), 128.2 (*Ar*), 125.9 (*Ar*), 125.8 (*Ar*), 99.3 (C=*C*H *exo*-**334b**), 95.9 (C=*C*H *endo*-**334b**), 89.3 (*C*OCH), 89.3 (*C*OCH), 79.9 (CO*C*H *exo*-**334b**), 78.2 (CO*C*H *endo*-**334b**), 66.7 (O*C*H_2 *exo*-**334b**), 65.8 (O*C*H_2 *endo*-**334b**), 54.3 (*C*HC(O) *exo*-**334b**), 51.0 (OCH*C*HCH *endo*-**334b**), 49.5 (OCHCH*C*H *endo*-**334b**),

49.1 (*C*HC(O) *exo*-**334b**), 42.1 (N*C*H$_2$), 41.9 (N*C*H$_2$), 31.9 (*C*H$_2$), 30.6 (*C*H$_2$), 30.3 (*C*H$_2$), 29.3 (*C*H$_2$), 21.1 (Ar*C*H$_3$), 21.1 (Ar*C*H$_3$), 14.3 (CH$_2$*C*H$_3$), 14.2 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 418.2020; $C_{26}H_{28}NO_4$ requires 418.2018.

(3a*S*,4*R*,7*R*,7a*R*)-2-Cyclopropyl-5-ethoxy-4-phenethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*endo*-334c) and (3a*R*,4*R*,7*R*,7a*S*)-2-Cyclopropyl-5-ethoxy –4-phenethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (e*xo*-334c)

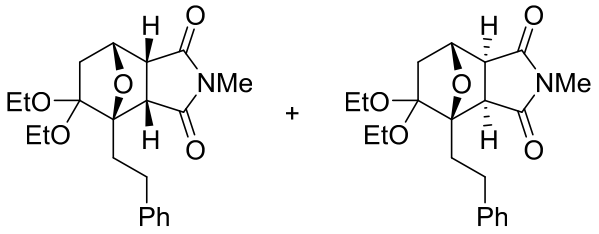


endo-**334c** *exo*-**334c**

Prepared from furan **325a** (108 mg, 0.500 mmol) and imide **329b** according to the General Cycloaddition Procedure over 4 h to give a mixture of the *cantharimides* **334c** as a pale wax (153 mg, 0.433 mmol, 87%, *endo*:*exo* = 60:40); R_f = 0.69 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2977s (C-H), 1775m, 1707s (C=O), 1401s; ^{1}H NMR (600 MHz; $CDCl_3$) 7.34–7.18 (5H, m, Ar*H*, *endo*-**334c**; 5H, m, Ar*H*, *exo*-**334c**), 5.19 (1H, dd, *J* = 5.4, 2.0, COC*H endo*-**334c**), 5.17 (1H, d, *J* = 2.0, COC*H exo*-**334c**), 5.11 (1H, d, *J* = 2.0, C=C*H exo*-**334c**), 5.00 (1H, d, *J* = 2.0, C=C*H endo*-**334c**), 3.92–3.75 (1H, m, OCH*H*' *endo*-**334c**; 1H, m, OC*H*$_2$ *exo*-**334c**), 3.65–3.58 (1H, m, OCH*H*' *endo*-**334c**; 1H, m, OCHC*H*CH *endo*-**334c**), 3.15 (1H, d, *J* = 7.8, OCHCHC*H endo*-**334c**), 3.07 (1H, d, *J* = 7.8, C*H*C(O) *exo*-**334c**), 2.89–2.74 (2H, m, C*H*$_2$Ph *endo*-**334c**; 1H, m, OCH*H*' *endo*-**334c**; 2H, m, C*H*$_2$Ph *exo*-**334c**; 1H, m, C*H*C(O) *exo*-**334c**), 2.63–2.55 (1H, m, NC*H exo*-**334c**; 1H, m, C*H*H'CH$_2$Ph *endo*-**334c**), 2.50–2.46 (1H, m, NC*H endo*-**334c**), 2.42–2.34 (1H, m, C*H*H'CH$_2$Ph *exo*-**334c**), 2.31–2.17 (1H, m, CH*H*'CH$_2$Ph *endo*-**334c**; 1H, m, CH*H*'CH$_2$Ph *exo*-**334c**), 1.37 (3H, t, *J* = 7.1, CH$_2$C*H*$_3$ *exo*-**334c**), 1.34 (3H, t, *J* = 7.1, CH$_2$C*H*$_3$ *endo*-**334c**), 0.98–0.85 (2H, m, CH(C*H*$_2$)$_2$ *endo*-**334c**; 4H, m, CH(C*H*H')$_2$ *exo*-**334c**), 0.82–0.78 (2H, m, CH(CH*H*')$_2$ *exo*-**334c**); ^{13}C NMR (150 MHz; $CDCl_3$) 176.7 (*C*(O)), 175.9 (*C*(O)), 175.4 (*C*(O)), 174.4 (*C*(O)), 167.0 (*C*OEt), 164.1 (*C*OEt), 142.0 (*Ar*), 141.6 (*Ar*), 128.4 (*Ar*), 128.4 (*Ar*), 128.4 (*Ar*), 128.3 (*Ar*), 126.0 (*Ar*), 125.8 (*Ar*), 99.4 (C=*C*H *exo*-**334c**), 96.5 (C=*C*H *endo*-**334c**), 89.6 (*C*OCH), 89.3 (*C*OCH), 80.1 (CO*C*H), 78.2 (CO*C*H), 66.7 (O*C*H$_2$), 66.6 (O*C*H$_2$), 53.8 (*C*HC(O) *exo*-**334c**), 50.6

(OCH*C*HCH *endo*-**334c**), 49.0 (OCHCH*C*H *endo*-**334c**), 48.5 (*C*HC(O) *exo*-**334c**), 31.8 (*C*H_2), 30.7 (*C*H_2), 30.3 (*C*H_2), 29.3 (*C*H_2), 22.2 (N*C*H), 21.9 (N*C*H), 14.3 (CH_2CH_3), 14.3 (CH_2CH_3), 5.0 (NCH*C*H_2), 5.0 (NCH*C*H_2), 4.9 (NCH*C*H_2), 4.6 (NCH*C*H_2); HRMS (CI^+) found $[M+H]^+$ 354.1708; $C_{21}H_{24}NO_4$ requires 354.1705.

(3a*S*,4*R*,7*R*,7a*R*)-5,5-Diethoxy-2-methyl-4-phenethylhexahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*endo*-335) and (3a*R*,4*R*,7*R*,7a*S*)-5,5-Diethoxy-2-methyl-4-phenethylhexahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (*exo*-335)



endo-**335** *exo*-**335**

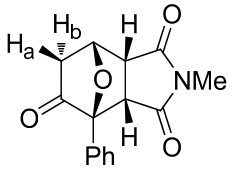
A solution of $[PPh_3AuNTf_2]_2PhMe$ (60 mg, 1.0 mol%, 2.0 mol% [Au]) in EtOH (1.9 mL) was added dropwise to a stirring solution of propargylic alcohol **316a** (1.00 g, 3.81 mmol) and *N*-methylmaleimide (0.508 g, 4.57 mmol) in EtOH (5.7 mL) at RT. The resulting solution was stirred for 16 h before being filtered through an aminopropyl cartridge, eluting with EtOAc. The filtrate was concentrated *in vacuo* to give the crude product (*endo*:*exo* = 70:30), which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give the *cantharimide endo*-**335** (276 mg, 0.740 mmol, 19%). Further elution of the column gave a mixture of the *cantharimides endo*-**335** and *exo*-**335** (528mg, 1.41 mmol, 37%). Further elution of the column gave the *cantharimide* e*xo*-**335** (228 mg 0.605 mmol, 16%).

***Cantharimide* endo-335**: Isolated as a white crystalline solid. m.p. = 123–125 °C; R_f = 0.61 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2973s (C-H), 1772w, 1697s (C=O), 1431s; ^{1}H NMR (400 MHz; $CDCl_3$) 7.34–7.28 (2H, m, Ar*H*), 7.26–7.18 (3H, m, Ar*H*), 4.75 (1H, t, *J* = 6.3, COC*H*), 3.67–3.62 (1H, m, OCHC*H*CH), 3.50–3.42 (2H, m, OCHCHC*H*; OC*H*H'), 3.27–3.21 (3H, m, OCH*H*'; O*C*H_2), 2.87–2.79 (4H, m, N*C*H_3; PhC*H*H'), 2.75–2.66 (1H, m, PhCH*H*'), 2.48–2.40 (1H, m, $PhCH_2CHH$'), 2.37–2.31 (1H, m, CH*H*'C$(OEt)_2$), 2.08–1.99 (1H, m, $PhCH_2CHH$'), 1.41 (1H, d, *J* = 13.7, CH*H*'$(OEt)_2$), 1.12 (3H, t, *J* = 7.1, CH_2CH_3), 0.95 (3H, t, *J* = 7.1, CH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) 175.8 (*C*(O)), 174.8 (*C*(O)), 142.4 (*Ar*), 128.9 (*Ar*), 128.6 (*Ar*), 126.3 (*Ar*), 107.6

(*C*(OEt)$_2$), 92.9 (*C*OCH), 75.4 (COC*H*), 58.3 (O*C*H$_2$), 55.9 (O*C*H$_2$), 52.4 (OCH*C*HCH), 49.8 (OCHCH*C*H), 38.9 (*C*H$_2$C(OEt)$_2$), 31.9 (*C*H$_2$), 30.1 (*C*H$_2$), 24.8 (N*C*H$_3$), 15.3 (CH$_2$*C*H$_3$), 15.2 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 374.1971; $C_{21}H_{28}NO_5$ requires 374.1968.

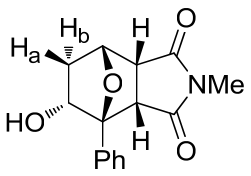
***Cantharimide* exo-335**: Isolated as a colorless oil. R_f = 0.48 (1:1 cyclohexane:EtOAc); ^{1}H NMR (400 MHz; $CDCl_3$); 7.38–7.16 (5H, m, Ar*H*), 4.82 (1H, d, *J* = 5.9, COC*H*), 3.29 (1H, d, *J* = 7.1, C*H*C(O)), 3.10 (1H, d, *J* = 7.1, C*H*C(O)), 3.03 (3H, s, NC*H*$_3$), 2.89–2.76 (1H, m, C*H*H'CH$_2$Ph), 2.63–2.44 (2H, m, CH*H*'C*H*H'Ph), 2.44–2.31 (1H, m, CH*H*'Ph; 1H, m, C*H*H'(OEt)$_2$), 1.71 (1H, d, *J* = 13.0, CH*H*'(OEt)$_2$), 1.27 (3H, t, *J* = 7.0, CH$_2$C*H*$_3$), 1.18 (3H, t, *J* = 7.1, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) 177.1 (*C*(O)), 177.0 (*C*(O)), 142.7 (*Ar*), 128.5 (*Ar*), 128.3 (*Ar*), 125.8 (*Ar*), 108.0 (*C*(OEt)$_2$), 91.4 (*C*OCH), 77.2 (CO*C*H), 58.5 (O*C*H$_2$), 57.5 (O*C*H$_2$), 51.2 (*C*HC(O)), 46.8 (*C*HC(O)), 41.4 (*C*H$_2$C(OEt)$_2$), 30.6 (*C*H$_2$), 29.4 (*C*H$_2$), 25.1 (N*C*H$_3$), 15.3 (CH$_2$*C*H$_3$), 15.1 (CH$_2$*C*H$_3$).

(3a*S*,4*S*,7*R*,7a*R*)-2-Methyl-4-phenyltetrahydro-1*H*-4,7-epoxyisoindole-1,3,5(2*H*,6*H*)-trione (336)



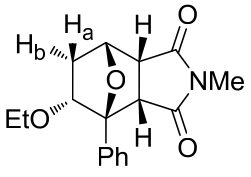
A solution of cantharimide *endo*-**330e** (290 mg, 0.970 mmol) in EtOAc (5.0 mL) was loaded onto silica plug (SCX-2, 20 g), which was then washed with EtOAc after 10 minutes. The filtrate was concentrated *in vacuo* to give the crude product, which was treated with cyclohexane (5.0 mL), sonicated and filtered to give the *cantharimide* **336** as a white crystalline solid (210 mg, 0.775 mmol, 80%); m.p. 171–173 °C; R_f = 0.45 (2:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2988s (C-H), 1765s (C=O), 1694s (C=O), 1500s;. ^{1}H NMR (400 MHz; $CDCl_3$) 7.76–7.72 (2H, m, Ar*H*), 7.47–7.38 (3H, m, Ar*H*), 5.31 (1H, t, *J* = 6.0, OC*H*), 3.95 (1H, dd, *J* = 9.1, 6.0, OCHC*H*CH), 3.66 (1H, d, *J* = 9.1, PhCC*H*), 3.00 (3H, s, NC*H*$_3$), 2.85 (1H, dd, *J* = 18.3, 6.0, H_a), 4.32 (1H, d, *J* = 18.3, H_b); ^{13}C NMR (100 MHz; $CDCl_3$) 204.7 (*C*(O) ketone), 173.8 (*C*(O) imide), 172.3 (*C*(O) imide), 132.3 (*Ar*), 128.9 (*Ar*), 128.5 (*Ar*), 126.5 (*Ar*), 90.6 (Ph*C*O), 74.7 (CO*C*H), 53.2 (PhC*C*H), 51.5 (OCH*C*H), 41.7 (*C*H$_a$), 25.2 (N*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 272.0920; $C_{15}H_{14}NO_4$ requires 272.0923.

(3a*S*,4*S*,5*R*,7*R*,7a*R*)-5-Hydroxy-2-methyl-4-phenylhexahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (337)



$NaBH_4$ (35 mg, 0.92 mmol) was added portionwise to a stirring solution of cantharimide **336** (50 mg, 0.18 mmol) in MeOH (1.8 mL) at 0 °C. The resulting solution was stirred at 0 °C for 1 h, before being filtered through a silica plug, eluting with EtOAc. The solvent was removed *in vacuo* to give the crude product, which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give the *cantharimide* **337** as a white crystalline solid (35 mg, 0.13 mmol, 70%); m.p. = 185–187 °C; R_f = 0.43 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 3388s br. (O-H), 2943w (C-H), 1763m, 1685s (C=O); 1492s; ^{1}H NMR (400 MHz; $CDCl_3$) 7.88–7.80 (2H, m, Ar*H*), 7.51–7.42 (2H, m, Ar*H*), 7.42–7.35 (1H, m, Ar*H*), 4.98 (1H, t, *J* = 6.1, COC*H*), 4.28 (1H, dd, *J* = 9.7, 3.0, C*H*OH), 3.77 (1H, dd, *J* = 10.0, 6.1, 1.8, COCHC*H*), 3.50 (1H, d, *J* = 10.0, PhCC*H*C(O)), 3.06 (3H, s, NCH_3), 2.57 (1H, dddd, *J* = 13.8, 9.7, 6.1, 1.8, H_a), 1.96 (1H, br. s, O*H*), 1.63 (1H, dd, *J* = 13.8, 3.0 H_b); ^{13}C NMR (100 MHz; $CDCl_3$) 175.4 (*C*(O)), 175.1 (*C*(O)), 138.3 (*Ar*), 128.8 (*Ar*), 128.4 (*Ar*), 125.7 (*Ar*), 91.8 (Ph*C*), 79.5 (*C*OH), 77.7 (CO*C*H), 53.0 (COCH*C*H), 52.5 (PhC*C*HC(O)), 36.1 (CH_a), 25.0 (NCH_3); HRMS (CI$^+$) found $[M+H]^+$ 274.1075; $C_{15}H_{16}NO_4$ requires 274.1079.

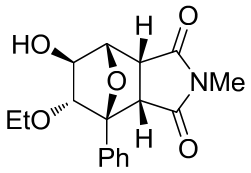
(3a*S*,4*S*,5*R*,7*R*,7a*R*)-5-Ethoxy-2-methyl-4-phenylhexahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (338)



A solution of cantharimide *endo*-**325e** (52 mg, 0.17 mmol) in EtOH (3.5 mL) was added to a flask primed with 10% Pd/C (30 mg, 0.28 mmol) at RT. The flask was placed under an atmosphere of hydrogen gas (1 atm.) and stirred at RT for 16 h, before the reaction mixture was filtered through Celite and the filtrate concentrated *in vacuo* to give the *cantharimide* **338** as a white crystalline solid (39 mg, 0.13 mmol, 76%); m.p. = 152–154 °C; R_f= 0.65 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2977s (C-H), 1775m, 1699s

(C=O), 1433s; ^{1}H NMR (400 MHz; $CDCl_3$) 7.83 (2H, d, *J* = 7.3, Ar*H*), 7.47–7.40 (2H, m, Ar*H*), 7.40–7.34 (1H, m, Ar*H*), 4.96 (1H, t, *J* = 6.1, COC*H*), 3.95 (1H, dd, *J* = 9.8, 3.2, C*H*OEt), 3.80–3.72 (1H, m, COCHC*H*CH), 3.52 (1H, d, *J* = 9.8, PhCC*H*C(O)), 3.38–3.29 (1H, m, OC*H*H'), 3.21–3.11 (1H, m, OCH*H*'), 3.04 (3H, s, NCH_3), 2.55–2.46 (1H, m, H_a), 1.66 (1H, dd, *J* = 13.7, 3.2, H_b), 1.04 (3H, t, *J* = 7.0, CH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) 175.3 (*C*(O)), 174.5 (*C*(O)), 139.3 (*Ar*), 128.5 (*Ar*), 128.1 (*Ar*), 126.0 (*Ar*), 91.4 (Ph*C*), 85.9 (*C*HOEt), 77.4 (CO*C*H), 66.8 (OCH_2), 53.0 (*C*HC(O)), 52.9 (*C*HC(O)), 35.6 (CH_a), 24.9 (NCH_3), 15.1 (CH_2CH_3); HRMS (CI$^+$) found $[M+H]^+$ 302.1399; $C_{17}H_{20}NO_4$ requires 302.1392.

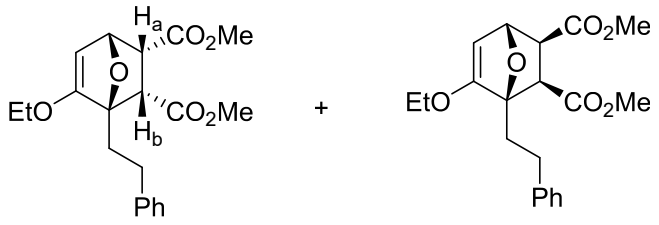
(3a*S*,4*S*,5*R*,6*S*,7*S*,7a*R*)-5-Ethoxy-6-hydroxy-2-methyl-4-phenylhexahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (339)



A solution of 9-BBN (0.50 M in THF, 1.7 mL, 0.85 mmol) was added dropwise to a stirring solution of cantharimide *endo*-**330e** (50 mg, 0.17 mmol) in anhydrous THF (0.85 mL) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 5 h before the reaction was treated with 2.0 M aq. NaOH (2.0 mL) and hydrogen peroxide (30% in water, 1.0 mL) at 0 °C. The resulting mixture was stirred at RT for 16 h before the reaction was quenched with 10% aq. $Na_2S_2O_3$ (10 mL) and extracted with EtOAc (3 × 20mL). The combined organic fractions were dried (phase separator) and concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give the *cantharimide* **339** as a white crystalline solid (28 mg 0.088 mmol, 52%); m.p. = 216–218 °C; R_f = 0.65 (1:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3447m br. (O-H), 2973w (C-H), 1774w, 1695s (C=O), 1434; ^{1}H NMR (400 MHz; DMSO-d_6) 7.77–7.70 (2H, m, Ar*H*), 7.47–7.41 (2H, m, Ar*H*), 7.40–7.34 (1H, m, Ar*H*), 5.65 (1H, d, *J* = 4.6, CO*H*), 4.61 (1H, dd, *J* = 7.0, 1.5, COC*H*), 3.78 (1H, dd, *J* = 9.7, 7.0, OCHC*H*C(O)), 3.67 (1H, dd, *J* = 4.6, 1.5, C*H*OH), 3.59–3.56 (1H, m, C*H*OEt), 3.39 (1H, d, *J* = 9.7, PhCC*H*C(O)), 3.27–3.19 (2H, m, OCH_2), 2.84 (3H, s, NCH_3), 0.95 (3H, t, *J* = 7.0, CH_2CH_3); ^{13}C NMR (100 MHz DMSO-d_6) 175.2 (*C*(O)), 174.3 (*C*(O)), 139.6 (*Ar*), 128.7 (*Ar*), 128.5 (*Ar*), 126.4 (*Ar*), 95.8 (*C*OEt), 90.3 (Ph*C*), 83.4 (PhCO*C*H), 76.1 (*C*HOH), 66.4 (OCH_2), 52.1 (PhC*C*HC(O)), 50.1 (OCH*C*HC(O)),

24.9 (N*C*H$_3$), 15.3 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 318.1342; $C_{17}H_{20}NO_5$ requires 318.1342; Weak (but real) ROE between C*H*OH and NC*H*$_3$; No significant ROE between C*H*OEt and NC*H*$_3$.

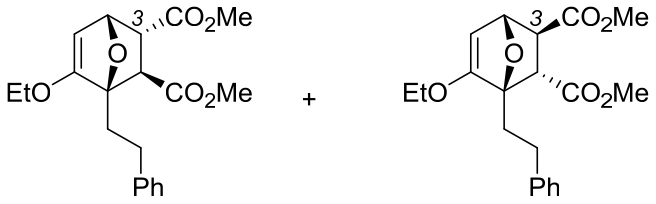
(1*R*,2*S*,3*R*,4*R*)-Dimethyl 6-ethoxy-1-phenethyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (*endo*-343a) and Dimethyl (1*R*,2*R*,3*S*,4*R*)-6-ethoxy-1-phenethyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (*exo*-343)



endo-**343** *exo*-**343**

Prepared from furan **325a** (108 mg, 0.500 mmol) and dimethyl maleate according to the General Cycloaddition Procedure over 3 days to give the crude product (*endo*:*exo* = 12:1), which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give a mixture of the *enol ethers* **343** as a colorless oil (125 mg, 0.347 mmol, 69%, *endo*:*exo* = 12:1); R_f = 0.32 (3:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2951s (C-H), 1739s (C=O), 1630s, 1435s; ^{1}H NMR (400 MHz; $CDCl_3$, *endo*-**343**) 7.35–7.19 (5H, m, Ar*H*), 5.34 (1H, d, *J* = 2.0, C=C*H*), 5.03 (1H, dd, *J* = 2.0, 3.9, COC*H*), 3.91–3.84 (1H, m, OC*H*H'), 3.78–3.72 (1H, m, OCH*H*'), 3.65 (3H, s, OC*H*$_3$), 3.64 (3H, s, OC*H*$_3$), 3.49 (1H, dd, *J* = 9.8, 3.9, C*H*$_a$), 3.31 (1H, dd, *J* = 9.8, C*H*$_b$), 2.88–2.74 (2H, m, C*H*$_2$Ph), 2.46–2.38 (1H, m, C*H*H'CH$_2$Ph), 2.20–2.12 (1H, m, CH*H*'CH$_2$Ph), 1.30 (3H, t, *J* = 7.1, CH$_2$C*H*$_3$); ^{1}H NMR (400 MHz; $CDCl_3$, *exo*-**343**) the following peaks in the ^{1}H NMR spectra indicate the presence of *exo*-**343**; 5.19 (1H, d, *J* = 2.0, COC*H*), 5.11 (1H, d, *J* = 2.0, C=C*H*). The remaining resonances were obscured by the major diastereoisomers and could not be full assigned; ^{13}C NMR (100 MHz; $CDCl_3$, *endo*-**343**) 171.2 (*C*(O)), 170.1 (*C*(O), 163.0 (*C*OEt), 142.1 (*Ar*), 128.4 (*Ar*), 125.9 (*Ar*), 99.2 (C=*C*H), 90.4 (*C*OCH), 78.3 (CO*C*H), 66.0 (O*C*H$_2$), 51.8 (*C*H or *C*H$_3$), 51.6 (*C*H or *C*H$_3$), 51.5 (*C*H or *C*H$_3$), 50.9 (*C*H or *C*H$_3$), 31.4 (*C*H$_2$), 30.6 (*C*H$_2$), 14.4 (*C*H$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 361.1654; $C_{20}H_{25}O_6$ requires 361.1651.

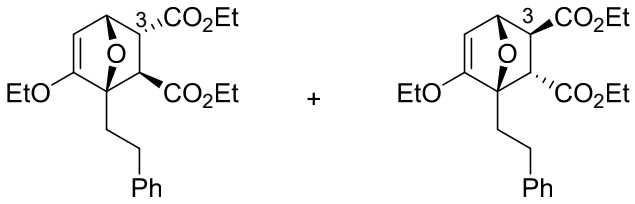
(1*R*,2*R*,3*R*,4*R*)-Dimethyl 6-oxo-1-phenethyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate (3-*endo*-344a) and (1*R*,2*S*,3*S*,4*R*)-Dimethyl 6-oxo-1-phenethyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate (3-*exo*-344a)



3-*endo*-**344a** 3-*exo*-**344a**

Prepared from furan **325a** (108 mg, 0.500 mmol) and dimethyl fumarate according to the General Cycloaddition Procedure over 4 h to give the crude product (3-*endo*-**344a**: 3-*exo*-**344a** = 20:80), which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give a mixture of the *enol ethers* **344a** as a colorless oil (139 mg, 0.386 mmol, 77%; 3-*endo*-**344a**: 3-*exo*-**344a** = 20:80); R_f = 0.39 (2:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2952s (C-H), 1736s (C=O), 1630s, 1436s; ^{1}H NMR (400 MHz; DMSO-d$_6$) 7.35–7.18 (5H, m, Ar*H* 3-*endo*-**344a**; 5H, m, Ar*H* 3-*exo*-**344a**), 5.20 (1H, dd, *J* = 4.5, 2.0, COC*H* 3-*endo*-**344a**), 5.18 (1H, d, *J* = 2.0, COC*H* 3-*exo*-**344a**), 5.11 (1H, d, *J* = 2.0, C=C*H* 3-*endo*-**344a**), 5.01 (1H, br. s, C=C*H* 3-*exo*-**344a**), 3.94–3.55 (6H, m, 2 × CO_2CH_3 3-*endo*-**344a**; 6H, m, 2 × CO_2CH_3 3-*exo*-**344a**; 2H, m, OCHC*H*C*H* 3-*endo*-**344a**; 2H, m, OCH_2 3-*endo*-**344a**; 2H, m, OCH_2 3-*exo*-**344a**), 3.20 (1H, d, *J* = 3.9, C*H*CO_2Me 3-*exo*-**344a**), 3.06 (1H, d, *J* = 3.9, C*H*CO_2Me 3-*exo*-**344a**), 2.78–2.69 (1H, m, PhC*H*H' 3-*exo*-**344a**), 2.66–2.54 (2H, m, PhCH_2 3-*endo*-**344a**; 1H, m, PhCH*H*' 3-*exo*-**344a**), 2.35–2.26 (1H, m, C*H*H'CH_2Ph 3-*exo*-**344a**), 2.20–2.08 (1H, m, C*H*H'CH_2Ph 3-*endo*-**344a**; 1H, m, CH*H*'CH_2Ph 3-*exo*-**344a**), 1.78–1.69 (1H, m, CH*H*'CH_2Ph 3-*endo*-**344a**), 1.25 (3H, t, *J* = 7.0, CH_2CH_3 3-*endo*-**344a**), 1.19 (3H, t, *J* = 7.1, CH_2CH_3 3-*exo*-**344a**);^{13}C NMR (100 MHz; DMSO-d$_6$) 172.7 (*C*(O)), 172.1 (*C*(O)), 171.3 (*C*(O)), 170.8 (*C*(O)), 165.6 (*C*OEt), 163.4 (*C*OEt), 142.1 (*Ar*), 142.0 (*Ar*), 128.9 (*Ar*), 128.8 (*Ar*), 128.6 (*Ar*), 128.5 (*Ar*), 126.4 (*Ar*), 126.3 (*Ar*), 100.3 (C=*C*H), 99.3 (C=*C*H), 90.7 (*C*OCH), 89.4 (*C*OCH), 80.6 (CO*C*H), 78.4 (CO*C*H), 66.9 (OCH_2), 66.4 (OCH_2), 54.2 (*C*H or CH_3), 52.6 (*C*H or CH_3), 52.5 (*C*H or CH_3), 52.4 (*C*H or CH_3), 50.6 (*C*H), 50.4 (*C*H), 31.2 (CH_2), 31.0 (CH_2), 30.6 (CH_2), 30.0 (CH_2), 14.6 (CH_2CH_3), 14.3 (CH_2CH_3); HRMS (CI$^+$) found $[M+H]^+$ 361.1658; $C_{20}H_{25}O_6$ requires 361.1651.

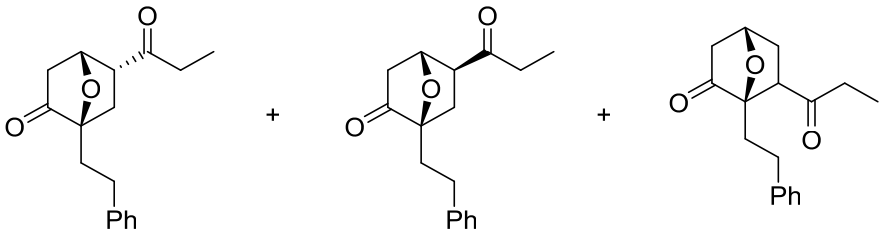
(1*R*,2*R*,3*R*,4*R*)-Diethyl 6-oxo-1-phenethyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate (3-*endo*-344b) and (1*R*,2*S*,3*S*,4*R*)-Diethyl 6-oxo-1-phenethyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate (3-*exo*-344b)



3-*endo*-**344b** 3-*exo*-**344b**

Prepared from furan **325a** (108 mg, 0.500 mmol) and diethyl fumarate according to the General Cycloaddition Procedure over 4 h to give the crude product (3-*endo*-**344b**: 3-*exo*-**344b** = 15:85), which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give a mixture of the *enol ethers* **344b** as a colorless oil (172 mg, 0.443 mmol, 89%, 3-*endo*-**344b**: 3-*exo*-**344b** = 15:85); R_f = 0.83 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2981s (C-H), 1731s (C=O), 1629s; ^{1}H NMR (400 MHz; MeOH-d$_4$) 7.31–7.14 (5H, m, Ar*H* 3-*endo*-**344b**; 5H, m, Ar*H* 3-*exo*-**344b**), 5.18 (1H, d, *J* = 2.0, C=C*H* 3-*exo*-**344b**), 5.14 (1H, dd, *J* = 4.4, 2.0, COC*H* 3-*endo*-**344b**), 5.11–5.08 (1H, m, C=C*H* 3-*endo*-**344b**; 1H, m, COC*H* 3-*exo*-**344b**), 4.25–4.03 (4H, m, CO$_2$C*H*$_2$ 3-*endo*-**344b**; 4H, m, CO$_2$C*H*$_2$ 3-*exo*-**344b**), 3.87–3.76 (1H, m, OCHC*H*CH 3-*endo*-**344b**; 2H, m, C=COC*H*$_2$ 3-*endo*-**344b**; 2H, m, C=COC*H*$_2$ 3-*exo*-**344b**), 3.29 (1H, d, *J* = 3.7, C*H*C(O) 3-*exo*-**344b**), 3.14 (1H, d, *J* = 3.7, C*H*C(O) 3-*exo*-**344b**), 2.92 (1H, d, *J* = 4.4, OCHCHC*H* 3-*endo*-**344b**), 2.86–2.65 (2H, m, C*H*$_2$Ph 3-*endo*-**344b**; 2H, m, C*H*$_2$Ph 3-*exo*-**344b**), 2.46–2.39 (1H, m, C*H*H'CH$_2$Ph 3-*exo*-**344b**), 2.29–2.17 (1H, m, C*H*H'CH$_2$Ph 3-*endo*-**344b**; CH*H*'CH$_2$Ph 3-*exo*-**344b**), 1.86–1.78 (1H, m, CH*H*'CH$_2$Ph 3-*endo*-**344b**), 1.38–1.20 (9H, m, CH$_2$C*H*$_3$ 3-*endo*-**344b**; 9H, m, CH$_2$C*H*$_3$ 3-*exo*-**344b**); ^{13}C NMR (100 MHz; CDCl$_3$) 172.6 (*C*(O)), 172.2 (*C*(O)), 171.0 (*C*(O)), 170.5 (*C*(O)), 165.9 (*C*OEt), 162.8 (*C*OEt), 142.0 (*Ar*), 141.9 (*Ar*), 128.1 (*Ar*), 128.0 (*Ar*), 127.9 (*Ar*), 127.8 (*Ar*), 125.6 (*Ar*), 125.5 (*Ar*), 99.2 (C=*C*H), 98.2 (C=*C*H), 90.9 (*C*OCH), 89.4 (*C*OCH), 80.9 (COC*H*), 78.5 (COC*H*), 66.4 (OC*H*$_2$), 65.9 (OC*H*$_2$), 60.8 (OC*H*$_2$), 60.8 (OC*H*$_2$), 60.7 (OC*H*$_2$), 60.6 (OC*H*$_2$), 54.3 (*C*HC(O)), 52.6 (*C*HC(O)), 50.2 (*C*HC(O)), 50.1 (*C*HC(O)), 31.2 (*C*H$_2$), 30.6 (*C*H$_2$), 30.2 (*C*H$_2$), 30.0 (*C*H$_2$), 13.3 (CH$_2$*C*H$_3$), 13.2 (CH$_2$*C*H$_3$), 13.2 (CH$_2$*C*H$_3$), 13.2 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 389.1967; $C_{22}H_{29}O_6$ requires 389.1964.

(1*R*,4*R*,5*R*)-1-Phenethyl-5-propionyl-7-oxabicyclo[2.2.1]heptan-2-one (*endo*-345), (1*R*,4*R*,5*S*)-1-Phenethyl-5-propionyl-7-oxabicyclo[2.2.1]heptan-2-one (*exo*-345) and (1*R*,4*S*)-1-Phenethyl-6-propionyl-7-oxabicyclo[2.2.1]heptan-2-one (345')

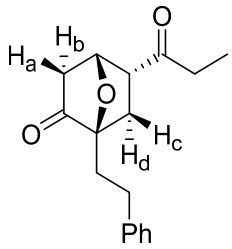


endo-**345** *exo*-**345** **345'**

Pent-1-en-3-one (49 µl, 0.50 mmol) was added to a stirring solution of furan **325a** (54 mg, 0.25 mmol) in DMC (0.25 mL) in a sealed tube at RT. The resulting reaction mixture was stirred at 80 °C for 16 h before the reaction was allowed to cool to RT. The reaction mixture was filtered through a silica plug (SCX-2, 10 g) with EtOAc and the filtrate concentrated *in vacuo* to give the crude product (*endo*-**345**: *exo*-**345**: **345'** = 60:40:5), which was purified by flash column chromatography (0 to 100% TBME:cyclohexane) to give a mixture of the *ketones* **13** as a colorless oil (22 mg, 0.081 mmol, 32%, *endo*-**345**: *exo*-**345**: **345'** = 10:3:1, fraction A). Further elution of the column gave a second fraction of the *ketones* **13** as a colorless oil (19 mg, 0.070 mmol, 28%, *endo*-**345**: *exo*-**345**: **345'** = 1:12:1, fraction B); R_f = 0.47 (4:1 hexane:EtOAc); ν_{max} (film/cm^{-1}) 2939s (C-H), 1756s (C=O), 1715s (C=O), 1456s; HRMS (CI$^+$) found [M+H]$^+$ 273.1493; $C_{17}H_{21}O_3$ requires 273.1491.

The three title compounds were not fully separated from each other. The following NMR assignments are based upon analysis of fractions A and B.

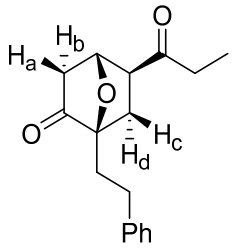
***Ketone endo*-345:**



^{1}H NMR (600 MHz; DMSO-d_6) 7.30–7.26 (2H, m, Ar*H*), 7.22–7.16 (3H, m, Ar*H*), 5.13 (1H, t, *J* = 5.1, COC*H*), 3.60–3.57 (1H, m, C*H*C(O)), 2.76–2.70 (1H, m, PhC*H*H'), 2.60–

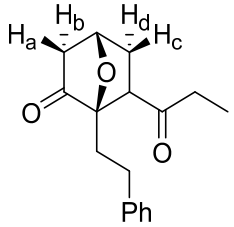
2.45 (3H, m, C*H*$_2$CH$_3$; PhCH*H*'), 2.48 (1H, dd, *J* = 17.7, 5.1, *H*$_a$), 2.09–1.96 (2H, m, PhCH$_2$C*H*$_2$), 1.96 (1H, d, *J* = 17.7, *H*$_b$), 1.93 (1H, dd, *J* = 13.2, 4.9, *H*$_d$), 1.86 (1H, dd, *J* = 13.2, 10.5, *H*$_c$), 0.93 (3H, t, *J* = 7.2, CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 211.0 (*C*(O)), 208.7 (*C*(O)), 141.6 (*Ar*), 128.4 (*Ar*), 128.1 (*Ar*), 125.9 (*Ar*), 88.5 (*C*OCH), 74.9 (CO*C*H), 53.9 (*C*HC(O)Et), 40.9 (*C*H$_a$), 35.5 (*C*H$_2$CH$_3$), 30.8 (*C*H$_c$), 30.5 (PhCH$_2$*C*H$_2$), 29.8 (Ph*C*H$_2$), 7.4 (CH$_2$*C*H$_3$).

***Ketone exo*-345:**



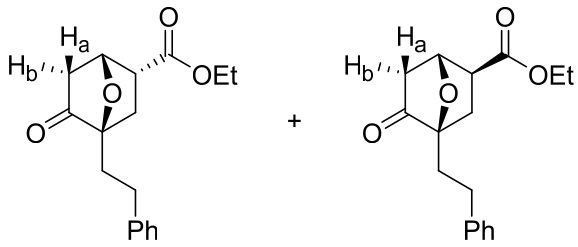
^{1}H NMR (400 MHz; MeOH-d$_4$) 7.34–7.11 (5H, m, Ar*H*), 5.02 (1H, d, *J* = 6.1, COC*H*), 3.15 (1H, dd, *J* = 9.0, 4.9, C*H*C(O)), 2.81 (1H, ddd, *J* = 13.6, 11.7, 5.5, PhC*H*H'), 2.74–2.49 (4H, m, C*H*$_2$CH$_3$; PhCH*H*'; *H*$_a$), 2.30 (1H, d, *J* = 17.6, *H*$_b$), 2.20–2.02 (3H, m, PhCH$_2$C*H*$_2$; *H*$_c$), 1.80 (1H, dd, *J* = 13.2, 9.0, *H*$_d$), 1.08 (3H, t, *J* = 7.2, CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz; MeOH-d$_4$) 212.0 (*C*(O)), 209.6 (*C*(O)), 141.8 (*Ar*), 128.0 (*Ar*), 127.9 (*Ar*), 125.6 (*Ar*), 87.7 (*C*OCH), 76.3 (CO*C*H), 54.2 (*C*HC(O)), 43.7 (*C*H$_a$), 33.5 (*C*H$_2$CH$_3$), 30.8 (*C*H$_c$), 30.5 (PhCH$_2$*C*H$_2$), 30.0 (Ph*C*H$_2$), 6.7 (CH$_2$*C*H$_3$).

***Ketone exo*-345':**



^{1}H NMR (600 MHz; DMSO-d$_6$) 4.94 (1H, t, *J* = 5.7, COC*H*), 2.90 (1H, dd, *J* = 8.7, 5.3, C*H*C(O)), 2.50 (1H, dd, *J* = 17.7, 5.7, *H*$_a$), 2.29 (1H, d, *J* = 17.7, *H*$_b$), 2.21–2.17 (1H, m, *H*$_c$), 1.96 (1H, dd, *J* = 12.4, 8.7, *H*$_d$), 0.87 (3H, t, *J* = 7.2, CH$_2$C*H*$_3$); remaining peaks obscured by the major products.

Ethyl (1*R*,2*R*,4*R*)-5-oxo-4-phenethyl-7-oxabicyclo[2.2.1]heptane-2-carboxylate (*endo*-352) and Ethyl (1*R*,2*S*,4*R*)-5-oxo-4-phenethyl-7-oxabicyclo[2.2.1]heptane-2-carboxylate (*exo*-352)



endo-**352** *exo*-**352**

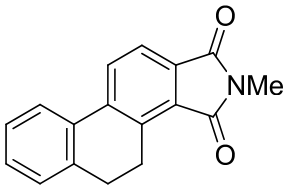
A solution of $HfCl_4$ (1.6 mg, 2.0 mol%) in DMC (0.06 mL) was added dropwise to a stirring solution of ethyl acrylate (41 μL, 38 mg, 0.38 mmol) and furan **325a** (54 mg, 0.25 mmol) in DMC (0.18 mL). The resulting solution was stirred at RT for 6 h before it was filtered through a silica plug (SCX-2, 10 g) with EtOAc and the filtrate concentrated *in vacuo* to give a mixture of the *enol ethers* **352** as a colorless oil (64 mg, 0.22 mmol, 89%, *endo*:*exo* = 70:30; no evidence for a minor regioisomer); R_f = 0.73 (1:1 cyclohexane:EtOAc); ν_{max} (film/cm^{-1}) 2938s (C-H), 1762s (C=O), 1730s (C=O), 1604m, 1493m, 1454s; HRMS (ESI^+) found $[M+H]^+$ 289.1437; $C_{17}H_{21}O_4$ requires 289.1434. In order to aid characterisation a sample of the mixed product was separated by Mass Directed Automated Purification to give the two diastereoisomers.

***Ketone endo*-352**: ^1H NMR (600 MHz; $CDCl_3$) 7.35–7.21 (2H, m, Ar*H*), 7.26 (2H, d, *J* = 7.0, Ar*H*), 7.25–7.22 (1H, m, Ar*H*), 5.01 (1H, t, *J* = 5.4, COC*H*), 4.22 (2H, q, *J* = 7.2, OCH_2), 3.40 (1H, dt, *J* = 11.2, 5.4, C*H*CO_2Et), 2.85 (1H, td, *J* = 12.9, 5.0, PhC*H*H'), 2.71 (1H, td, *J* = 12.9, 5.0, PhCH*H*'), 2.57 (1H, dd, *J* = 17.8, 5.4, H_a), 2.38 (1H, d, *J* = 17.8, H_b), 2.29 (1H, ddd, *J* = 14.4, 12.9, 5.0, PhCH_2C*H*H'), 2.18–2.12 (2H, m, PhCH_2CH*H*', C*H*H'CHCO_2Et), 2.08–2.02 (1H, m, CH*H*'CHCO_2Et), 1.32 (3H, t, *J* = 7.2, CH_2CH_3); ^{13}C NMR (150 MHz; $CDCl_3$) 210.2 (*C*O_2Et), 171.3 (*C*(O)), 141.6 (*Ar*), 128.4 (*Ar*), 128.3 (*Ar*), 126.0 (*Ar*), 88.9 (*C*OCH), 75.6 (CO*C*H), 61.2 (O*C*H_2), 47.3 (*C*HCO$_2$Et), 41.4 (C(O)*C*H_2), 32.8 (*C*H_2CHCO$_2$Et), 30.9 (*C*H_2CH_2Ph), 30.2 (*C*H_2Ph), 14.2 (CH$_2$*C*H_3); No ROE between H_b and C*H*CO_2Et.

***Ketone exo*-352**: ^1H NMR (600 MHz; $CDCl_3$) 7.31–7.27 (2H, m, Ar*H*), 7.24–7.21 (2H, m, Ar*H*), 7.21–7.17 (1H, m, Ar*H*), 5.10 (1H, d, *J* = 6.1, COC*H*), 4.23 (2H, q, *J* = 7.2, OCH_2), 2.88 (1H, dd, *J* = 9.2, 4.8, C*H*CO_2Et), 2.83 (1H, td, *J* = 12.9, 5.0, PhC*H*H'), 2.67

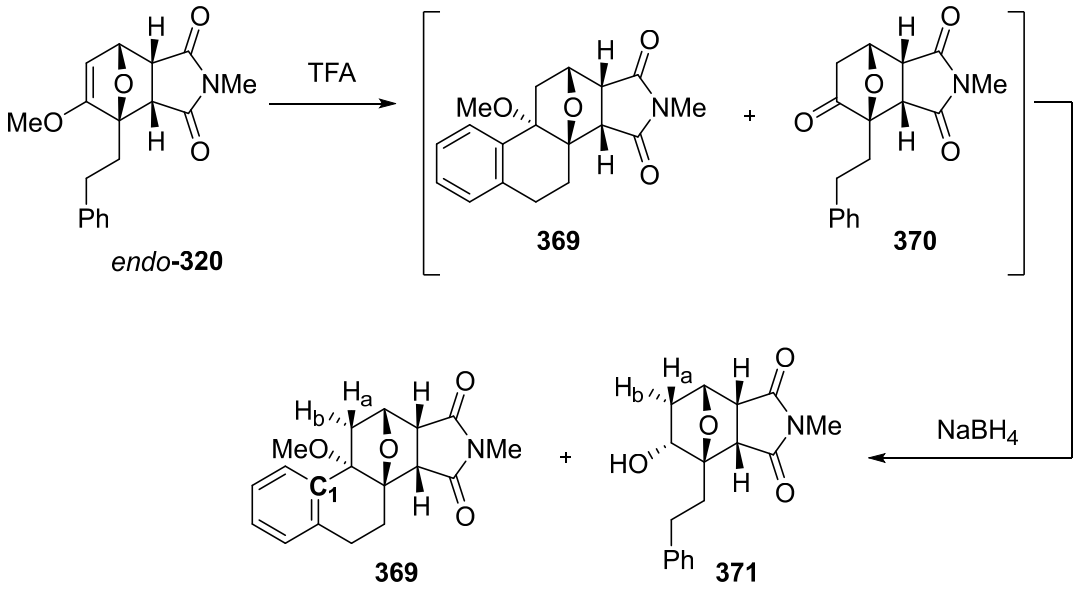
(1H, td, *J* = 12.9, 5.0, PhCH*H*'), 2.59 (1H, dd, *J* = 17.2, 6.1, H_a), 2.28–2.14 (4H, m, $PhCH_2CH_2$', H_b, C*H*H'$CHCO_2Et$), 1.90 (1H, dd, *J* = 13.6, 9.2, CH*H*'$CHCO_2Et$), 1.31 (3H, t, *J* = 7.2, CH_2CH_3); (150 MHz; $CDCl_3$) 211.2 (*C*(O)), 172.3 (*C*(O)), 141.6 (*Ar*), 128.4 (*Ar*), 128.4 (*Ar*), 126.0 (*Ar*), 88.0 (*C*OCH), 77.3 (CO*C*H), 61.4 (OCH_2), 47.9 ($CHCO_2Et$), 44.2 ($C(O)CH_2$), 32.4 (CH_2CHCO_2Et), 30.6 ($PhCH_2CH_2$), 30.3 ($PhCH_2$), 14.2 (CH_2CH_3); ROE between H_b and C*H*CO_2Et.

2-Methyl-4,5-dihydro-1*H*-naphtho[2,1-e]isoindole-1,3(2*H*)-dione (364)



A solution of Tf_2O (43 μL, 73 mg, 0.43 mmol) in CH_2Cl_2 (0.25 mL) was added to a stirring solution of cantharimide *endo*-**330a** (28 mg, 0.086 mmol) in CH_2Cl_2 (0.25 mL). The reaction was stirred for 16 h before the reaction was cooled to 0 °C and quenched with aq. sat. $NaHCO_3$ (10 mL) and diluted with CH_2Cl_2 (10 mL). The aq. extract was washed with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. This was purified by flash column chromatography (2:1 petrol 40–60 °C:EtOAc) to give *phthalimide* **364** as a white crystalline solid (7 mg, 0.027 mmol, 31%); m.p. 160–162 °C; R_f = 0.40 (8:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2942s (C-H), 1765s, 1705s (C=O), 1479s; ^{1}H NMR (600 MHz; $CDCl_3$) 8.02 (1H, d, *J* = 7.9, Ar*H*), 7.78–7.75 (2H, m, Ar*H*), 7.37–7.32 (2H, m, Ar*H*), 7.31–7.29 (1H, m, Ar*H*), 3.44 (2H, t, *J* = 7.2, CH_2), 3.18 (3H, s, CH_3), 2.91 (2H, t, *J* = 7.2, CH_2); ^{13}C NMR (150 MHz; $CDCl_3$) 169.5 (*C*(O)), 168.4 (*C*(O)), 141.3 (*Ar*), 138.0 (*Ar*), 137.3 (*Ar*), 132.8 (*Ar*), 131.1 (*Ar*), 129.3 (*Ar*), 128.6 (*Ar*), 128.5 (*Ar*), 127.5 (*Ar*), 124.7 (*Ar*), 121.8 (*Ar*), 27.9 (CH_2), 24.0 (CH_3), 23.1 (CH_2); HRMS (CI^+) found $[M]^+$ 263.0949; $C_{17}H_{13}NO_2$ requires 263.0946.

(3a*S*,3b*R*,9b*S*,11*R*,11a*R*)-9b-Methoxy-2-methyl-4,5,9b,10,11,11a-hexahydro-3b,11-epoxynaphtho[2,1-e]isoindole-1,3(2*H*,3a*H*)-dione (369) and (3a*S*,4*R*,5*R*,7*R*,7a*R*)-5-Hydroxy-2-methyl-4-phenethylhexahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (371)

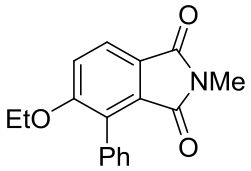


TFA (0.50 mL) was added to a stirring solution of cantharimide *endo*-**320** (46 mg, 0.15 mmol) in CH_2Cl_2 (1.0 mL) at –78°C. The reaction was allowed to reach RT and stirred for 16 h before the reaction was quenched with aq. sat. $NaHCO_3$ (10 mL) and diluted with CH_2Cl_2 (10 mL). The aq. extract was washed with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product (**369**:**370** = 3:1). This was partially purified by flash column chromatography (2:1 petrol 40–60 °C:EtOAc) to give a mixture of **369** and **370** (3:1). The mixture of products was then dissolved in hot MeOH (2.0 mL), cooled to 0 °C and treated with $NaBH_4$ (10 mg, 0.31 mmol). The resulting suspension was stirred at 0 °C for 4 h before the reaction was diluted with CH_2Cl_2 (10 mL) and treated with Amberlyst IRA743 boron scavenger (*ca*. 100 mg). The mixture was filtered and the solution concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (2:1 petrol 40–60 °C:EtOAc) to give the *cantharimide* **369** as a white crystalline solid (32 mg, 0.10 mmol, 69%); m.p. 174–176 °C; R_f = 0.55 (1:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2934s (C-H), 1771s, 1693s (C=O), 1434s; ^{1}H NMR (600 MHz; $CDCl_3$) 7.27–7.22 (2H, m, Ar*H*), 7.19 (1H, t, *J* = 7.1, Ar*H*), 7.10 (1H, d, *J* = 7.7, Ar*H*), 4.77 (1H, t, *J* = 6.2, OC*H*), 3.71 (1H, dd, *J* = 9.8, 6.2, OCHC*H*), 3.16 (1H, d, *J* = 9.8, OCHCHC*H*), 3.02–2.96 (4H, m, NCH_3; ArC*H*H'), 2.85 (1H, dd, *J* = 16.6, 5.7,

ArCH*H*'), 2.76 (3H, s, OCH_3), 2.53 (1H, dd, *J* = 13.8, 6.2, H_a), 2.43 (1H, td, *J* = 14.2, 6.0, ArCH$_2$C*H*H'), 2.34 (1H, dd, *J* = 14.2, 6.0, ArCH$_2$CH*H*'), 2.25 (1H, d, *J* = 13.8, H_b); ^{13}C NMR (150 MHz; $CDCl_3$) 175.5 (*C*(O)), 174.7 (*C*(O)), 138.3 (***C*****$_1$**), 135.8 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 127.6 (*Ar*), 127.5 (*Ar*), 91.2 (*C*OCH), 82.7 (MeO*C*), 76.9 (CO*C*H), 54.6 (OCH*C*H), 54.3 (OCHCH*C*H), 53.1 (O*C*H$_3$), 46.7 (*C*H$_a$), 28.4 (Ar*C*H$_2$), 26.0 (ArCH$_2$*C*H$_2$), 25.0 (N*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 314.1382; $C_{18}H_{20}NO_4$ requires 314.1387. A HMBC experiment measured $^3J_{CH}$ (**C$_1$**, H$_a$) = 5.0 Hz (torsion angle *ca*. 0°); $^3J_{CH}$ (**C$_1$**, H$_b$) = 1.0 Hz (torsion angle *ca*. 120°).

Further elution of the column gave the *cantharimide* **371** as a colorless oil (8 mg, 0.027 mmol, 18%); R$_f$ = 0.23 (1:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 3445s (O-H), 2927s (C-H), 1771s, 1691s (C=O), 1434s; ^{1}H NMR (600 MHz; $CDCl_3$) 7.31 (2H, t, *J* = 7.4, Ar*H*), 7.27 (2H, d, *J* = 7.4, Ar*H*), 7.22 (1H, t, *J* = 7.2, Ar*H*), 4.77 (1H, t, *J* = 6.1, OC*H*), 4.23 (1H, m, C*H*OH), 3.64 (1H, dd, *J* = 9.7, 6.1, OCHC*H*), 3.20 (1H, d, *J* = 9.7, OCHCHC*H*), 3.00–2.88 (4H, m, NCH_3; PhC*H*H'), 2.42–2.27 (3H, m, BnCH_2; H_a), 1.98–1.95 (1H, m, O*H*), 1.49 (1H, dd, *J* = 13.8, 3.0, H_b), 1.25 (1H, m, PhCH*H*'); ^{13}C NMR (150 MHz; $CDCl_3$) 175.8 (*C*(O)), 175.7 (*C*(O)), 141.2 (*Ar*), 128.8 (*Ar*), 128.4 (*Ar*), 126.4 (*Ar*), 90.8 (BnCH$_2$*C*), 77.7 (O*C*HCH), 75.5 (*C*OH), 52.8 (OCH*C*H), 51.9 (OCHCH*C*H), 36.8 (HOCH*C*H$_2$), 35.0 (Bn*C*H$_2$), 30.0 (Ph*C*H$_2$), 24.9 (N*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 302.1385; $C_{17}H_{20}NO_4$ requires 302.1387.

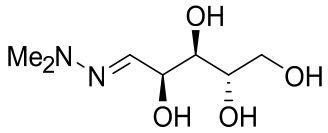
5-Ethoxy-2-methyl-4-phenylisoindoline-1,3-dione (368)



A solution of propargylic alcohol **316e** (100 mg, 0.427 mmol) in EtOH (1.0 mL) was treated with *N*-methylmaleimide (57 mg, 0.51 mmol) and [PPh$_3$AuNTf$_2$]$_2$PhMe (7 mg, 0.043 mmol, 2.0 mol% [Au]) at RT. The resulting solution was stirred at RT for 9 h before it was filtered through a silica plug, eluting with EtOAc, and the filtrate concentrated *in vacuo* to give the crude intermediate. This was then treated with EtOH (0.20 mL) and MsOH (2.0 mL) at RT and stirred for 16 h. The reaction was then diluted with water (30 mL) and EtOAc (30 mL) and the aq. extract washed EtOAc (3 × 20 mL). The combined organic extracts were then washed with 10% aq. K_2CO_3 (50 mL) and brine

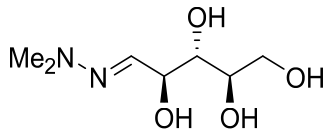
(50 mL), dried ($MgSO_4$) and concentrated. The concentrated material was then treated with EtOH (0.20 mL) and MsOH (2.0 mL) at RT and stirred for 16 h. The reaction was then diluted with water (30 mL) and EtOAc (30 mL) and the a. extract washed EtOAc (3 × 20 mL). The combined organic extracts were then washed with 10% aq. K_2CO_3 (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. This was purified by flash column chromatography (7:1 petrol 40–60 °C: EtOAc) to give the *phthalimide* **368** as a white crystalline solid (55 mg, 0.20 mmol, 47%); m.p. 93–95 °C; R_f = 0.31 (7:1 petrol 40–60 °C:EtOAc); ν_{max} (film/cm^{-1}) 2922s (C-H), 1764m (C=O), 1709s (C=O), 1466s; ^{1}H NMR (600 MHz; $CDCl_3$) 7.80 (1H, d, *J* = 8.2, Ar*H*), 7.46–7.40 (3H, m, Ar*H*), 7.38–7.36 (2H, m, Ar*H*), 7.15 (1H, d, *J* = 8.2, Ar*H*), 4.09 (2H, q, *J* = 6.8, O*CH*$_2$), 3.07 (3H, s, NC*H*$_3$), 1.32 (2H, t, *J* = 6.8, CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz; $CDCl_3$) 168.2 (*C*(O)), 167.8 (*C*(O)), 161.2 (*Ar*), 132.0 (*Ar*), 130.5 (*Ar*), 130.3 (*Ar*), 130.2 (*Ar*), 128.3 (*Ar*), 127.7 (*Ar*), 124.3 (*Ar*), 124.0 (*Ar*), 115.5 (*Ar*), 65.1 (O*C*H$_2$), 23.9 (N*C*H$_3$), 14.5 (CH$_2$*C*H$_3$); HRMS (CI$^+$) found [M]$^+$ 281.1047; $C_{17}H_{15}NO_3$ requires 281.1052.

(2*S*,3*R*,4*S*,*E*)-5-(2,2-Dimethylhydrazono)pentane-1,2,3,4-tetraol (441a)[247]



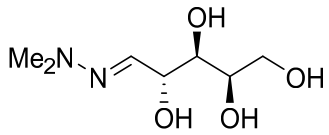
Prepared from L-arabinose (13.5 g, 90.0 mmol) according to the General Hydrazone Synthesis Procedure to give the hydrazone **441a** as a white crystalline solid (17.1 g, 89.5 mmol, 99%); m.p. = 93–95 °C (lit. m.p. = 88–90 °C)[247]; R_f = 0.24 (acetone); ν_{max} (film/cm^{-1}) 3420s (O-H), 3264s (O-H), 2938s (C-H), 1470s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 6.61 (1H, d, *J* = 6.2, *H*C=N), 4.61 (1H, d, *J* = 5.8, CHO*H*), 4.53 (1H, d, *J* = 5.7, CHO*H*), 4.42 (1H, d, *J* = 7.2, CHO*H*), 4.33 (1H, t, *J* = 5.6, CH$_2$O*H*), 4.23–4.19 (1H, m, N=CHC*H*), 3.66–3.55 (1H, m, C*H*H'OH), 3.51–3.46 (1H, m, C*H*CH$_2$OH), 3.41–3.33 (1H, m, CH*H*'OH; *H*OD), 3.31–3.27 (1H, m, N=CHCHC*H*), 2.67 (6H, s, N(C*H*$_3$)$_2$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 138.5 (*C*=N), 73.8 (*C*HCH$_2$OH), 71.2 (N=CHCH*C*H), 70.5 (N=CH*C*H), 63.5 (*C*H$_2$OH), 42.6 (N(*C*H$_3$)$_2$); [α]$_D$ (20 °C) = –44.0 (MeOH, C = 1.0); data in accordance with the literature.[247]

(2*R*,3*S*,4*S*,*E*)-5-(2,2-Dimethylhydrazono)pentane-1,2,3,4-tetraol (441b)



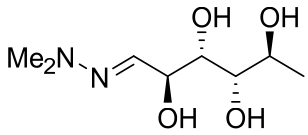
Prepared from D-ribose (1.00 g, 6.67 mmol) according to the General Hydrazone Synthesis Procedure to give the *hydrazone* **441b** as a white crystalline solid (1.26 g, 6.56 mmol, 98%); m.p. = 70–72 °C; R_f = 0.24 (acetone); ν_{max} (film/cm^{-1}) 3335s br. (O-H), 2992s (C-H), 1597s, 1469s, 1444s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 6.56 (1H, d, *J* = 6.4, N=C*H*), 4.85 (1H, d, *J* = 5.1, CHO*H*), 4.63 (1H, d, *J* = 5.3, CHO*H*), 4.48 (1H, d, *J* = 4.9, CHO*H*), 4.31 (1H, t, *J* = 5.7, CH$_2$O*H*), 4.12–4.09 (1H, m, N=CHC*H*), 3.57–3.54 (1H, m, C*H*H'), 3.46–3.35 (3H, m, CH*H*'C*H*C*H*), 2.67 (6H, s, N(C*H*$_3$)$_2$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 137.4 (N=*C*), 74.4 (*C*H), 72.3 (*C*H), 72.2 (*C*H), 63.2 (*C*H$_2$), 42.6 (N(*C*H$_3$)$_2$); HRMS (ESI$^+$) found [M+H]$^+$ 193.1180; $C_7H_{17}N_2O_4$ requires 193.1188; [α]$_D$ (20 °C) = –22.6 (MeOH, C = 1.0).

(2*R*,3*R*,4*R*,*E*)-5-(2,2-Dimethylhydrazono)pentane-1,2,3,4-tetraol (441c)



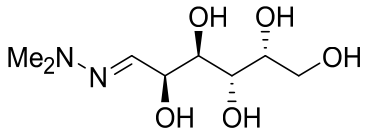
Prepared from D-lyxose (1.00 g, 6.67 mmol) according to the General Hydrazone Synthesis Procedure to give the *hydrazone* **441c** as a white crystalline solid (1.26 g, 6.56 mmol, 98%); m.p. = 73–75 °C; R_f = 0.14 (acetone); ν_{max} (film/cm^{-1}) 3336s br. (O-H), 2865s (C-H), 1599s, 1468s, 1443s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 6.56 (1H, d, *J* = 6.2, N=C*H*), 4.84 (1H, d, *J* = 5.3, CHO*H*), 4.45 (1H, t, *J* = 5.6, CH$_2$O*H*), 4.22 (1H, d, *J* = 6.6, CHO*H*)), 4.19 (1H, d, *J* = 7.2, CHO*H*), 4.01–3.96 (1H, m, N=CHC*H*), 3.66–3.62 (1H, m, C*H*CH$_2$), 3.43–3.38 (2H, m, N=CHCHC*H*, C*H*H'OH), 3.37–3.33 (1H, m, CH*H*'OH; *H*OD), 2.68 (6H, s, N(C*H*$_3$)$_2$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 138.5 (N=*C*), 72.8 (N=CHCH*C*H), 71.0 (N=CH*C*H), 70.3 (*C*HCH$_2$OH), 62.8 (*C*H$_2$OH), 42.6 (N(*C*H$_3$)$_2$); HRMS (ESI$^+$) found [M+H]$^+$ 193.1196; $C_7H_{17}N_2O_4$ requires 193.1188; [α]$_D$ (20 °C) = +16.4 (MeOH, C = 0.58).

(2*S*,3*S*,4*S*,5*S*,*E*)-1-(2,2-Dimethylhydrazono)hexane-2,3,4,5-tetraol (441e)



Prepared from L-rhamnose monohydrate (2.58 g, 14.2 mmol) according to the General Hydrazone Synthesis Procedure to give the *hydrazone* **441e** as a white crystalline solid (2.90 g, 14.1 mmol, 99%); m.p. = 101–103 °C; R_f = 0.30 (acetone); ν_{max} (film/cm^{-1}) 3347s br. (O-H), 2920w (C-H), 1611m, 1444s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 6.57 (1H, d, *J* = 6.0, N=C*H*), 4.82 (1H, d, *J* = 5.3, CHO*H*), 4.41 (1H, d, *J* = 5.6, CHO*H*), 4.12 (1H, d, *J* = 7.7, CHO*H*), 4.08 (1H, d, *J* = 7.2, CHO*H*), 3.98–3.93 (1H, m, N=CHC*H*), 3.64–3.60 (1H, m, N=CHCHC*H*), 3.59–3.53 (1H, m, C*H*CH$_3$), 3.32–3.29 (1H, m, C*H*CHCH$_3$), 2.66 (6H, s, N(C*H*$_3$)$_2$), 1.10 (3H, d, *J* = 6.2, CHC*H*$_3$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 138.8 (N=*C*), 73.5 (*C*H), 71.1 (*C*H), 71.0 (*C*H), 66.3 (*C*H), 42.6 (N(*C*H$_3$)$_2$), 20.8 (*C*H$_3$); HRMS (ESI$^+$) found [M+H]$^+$ 207.1347; $C_8H_{19}N_2O_4$ requires 207.1345; $[\alpha]_D$ (20 °C) = +4.1 (MeOH, C = 1.3).

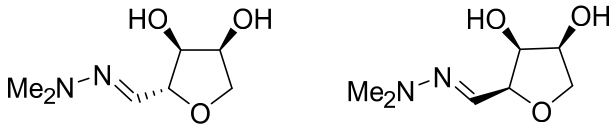
(2*R*,3*S*,4*R*,5*S*,*E*)-6-(2,2-Dimethylhydrazono)hexane-1,2,3,4,5-pentaol (441f)[247]



A stirring solution of D-galactose (1.80 g, 10.0 mmol) in MeOH (20 mL, 0.50 M) was treated with NH_2NMe_2 (1.5 mL, 1.2 g, 20 mmol) and Amberlyst 15 (2.00 g) at RT and the reaction stirred at RT for 3 days. The reaction was then filtered and the filtrate concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (acetone) to give the *hydrazone* **441f** as a yellow crystalline solid (680 mg, 3.06 mmol, 31%); m.p. = 106–108 °C (lit. m.p. = 96–100 °C)[247]; R_f = 0.20 (1:5 MeOH:acetone); ν_{max} (film/cm^{-1}) 3362s br. (O-H), 2931s (C-H), 1593s, 1469s, 1412s; ^{1}H NMR (600 MHz; DMSO-d$_6$) 6.65 (1H, d, *J* = 6.0, N=C*H*), 4.53 (1H, d, *J* = 6.4, CHO*H*), 4.43 (1H, t, *J* = 5.6, CH$_2$O*H*), 4.33 (1H, d, *J* = 7.5, CHO*H*), 4.27–4.24 (1H, m, N=CHC*H*), 4.14–4.10 (2H, m, 2 × CHO*H*), 3.70 (1H, dd, *J* = 6.5, 1.4, C*H*OH), 3.51–3.47 (1H, m, C*H*OH), 3.44–3.36 (3H, m, C*H*OH, C*H*$_2$OH), 2.67 (6H, s, N(C*H*$_3$)$_2$); ^{13}C NMR (150 MHz; DMSO-d$_6$) 139.0 (N=*C*), 72.5 (*C*H), 70.4 (*C*H), 69.9 (*C*H), 69.1 (*C*H), 63.1

(CH_2), 42.7 ($N(CH_3)_2$); $[\alpha]_D$ (20 °C) = –30.0 (MeOH, C = 1.0); Data in accordance with the literature. [247]

(2*R*,3*S*,4*S*)-2-((*E*)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (*anti*-443a) and (2*S*,3*S*,4*S*)-2-((*E*)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (*syn*-443a)



anti-**443a** *syn*-**443a**

Experiment A (6.60 mmol scale): Prepared from hydrazone **441a** (1.26 g, 6.60 mmol) according to the General Acid-Catalyzed Cyclization Procedure, to give the crude product (*anti*:*syn* = 75:25). This was purified by flash column chromatography (80:100 hexane:acetone) to give the *tetrahydrofuran* **443a** (772 mg, 4.44 mmol, 67%, *anti*:*syn* = 75:25).

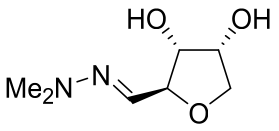
Experiment B (104 mmol scale): Prepared from hydrazone **441a** (20.0 g, 104 mmol) according to the General Acid-Catalyzed Cyclization Procedure, to give the crude product (*anti*:*syn* = 75:25). This was purified by flash column chromatography (80:100 hexane:acetone) to give a mixture of the *tetrahydrofuran anti*-**443a** and the *tetrahydrofuran syn*-**443a** (11.9 g, 68.3 mmol, 66%, *anti*:*syn* = 75:25).

***Tetrahydrofuran anti*-443a:** Isolated as a single stereoisomer following recrystallization from boiling CPME. Isolated as a white crystalline solid; m.p. = 65–67 °C; R_f = 0.33 (1:1 acetone:hexane); ν_{max} (film/cm^{-1}) 3415s br. (O-H), 2875s (C-H), 1586s, 1467s, 1445s; ^{1}H NMR (600 MHz; MeOH-d_4) 6.51 (1H, d, *J* = 6.6, N=C*H*), 4.23–4.18 (2H, m, N=CHC*H*, CH_2C*H*), 4.08 (1H, dd, *J* = 9.6, 4.9, OC*H*H'), 4.02 (1H, dd, *J* = 7.3, 5.1, N=CHCHC*H*), 3.76–3.72 (1H, m, OCH*H*'), 2.79 (6H, s, $N(CH_3)_2$); ^{13}C NMR (150 MHz; MeOH-d_4) 135.6 (*C*=N), 82.5 (*C*HCH$_2$), 76.5 (N=CHCH*C*H), 73.9 (O*C*H$_2$), 72.4 (CH_2CH*C*H), 42.8 ($N(CH_3)_2$); HRMS (EI$^+$) found $[M]^+$ 174.0979; $C_7H_{14}N_2O_3$ requires 174.0999; $[\alpha]_D$ (20 °C) = +85.8 (*anti*-**443a**, MeOH, C = 1.4).

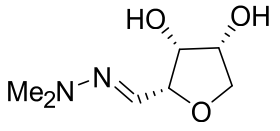
***Tetrahydrofuran syn*-433a**: ^{1}H NMR (600 MHz; MeOH-d_4) 6.71 (1H, d, *J* = 7.2, N=C*H*), 4.36–4.31 (2H, m, N=CHC*H*; CH_2C*H*), 4.15 (1H, t, *J* = 4.8, C*H*CHCH$_2$), 3.91 (1H, dd, *J* = 8.7, 6.2, OC*H*H'), 3.76–3.72 (1H, m, OCH*H*'), 2.79 (6H, s, $N(CH_3)_2$); ^{13}C NMR

(150 MHz; MeOH-d4) 135.6 (*C*=N), 83.1 (*C*HCH2), 74.3 (N=CHCH*C*H), 73.2 (N=CH*C*H), 72.5 (O*C*H2), 42.8 (N(*C*H3)2).

(2*S*,3*R*,4*R*)-2-((*E*)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (*ent-syn*-443a) and (2*R*,3*R*,4*R*)-2-((*E*)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (*ent-syn*-443a)



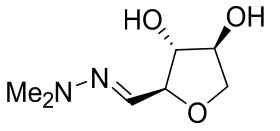
ent-anti-**443a**



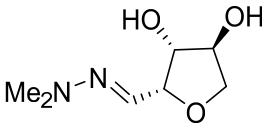
ent-syn-**443a**

Prepared from hydrazone **441b** (1.16 g, 6.03 mmol) according to General Acid-Catalyzed Cyclization Procedure to give the crude product (*anti*:*syn* = 75:25). This was purified by flash column chromatography (80:100 hexane:acetone) the *tetrahydrofuran* **433a** as a yellow oil (620 mg, 3.56 mmol, 59%, *anti*:*syn* = 75:25); ^{1}H NMR consistent with **433a**; $[\alpha]_D$ (20 °C) = –24.2 (*ent*-**433a**, MeOH, C = 1.1).

(2*R*,3*R*,4*S*)-2-((*E*)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (*anti*-433b) and ((2*S*,3*R*,4*S*)-2-((*E*)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (*syn*-433b)



anti-**433b**



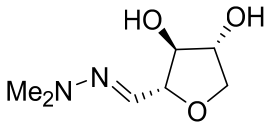
syn-**433b**

Method A: Prepared from hydrazone **441c** (1.22 g, 6.35 mmol) according to the General Acid-Catalyzed Cyclization Procedure to give the crude product (*d.r.* = 55:45). This was purified by flash column chromatography (80:100 hexane:acetone) to give the *tetrahydrofuran* **433b** (731 mg, 4.20 mmol, 66%, *d.r.* = 55:45).

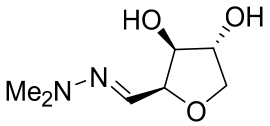
Method B: Prepared according to the General Hydrazone Synthesis Procedure from D-xylose (1.00 g, 6.67 mmol) to give a crude hydrazone, which was subjected to the General Acid-Catalyzed Cyclization Procedure to give the crude product (*d.r.* = 55:45). This was purified by flash column chromatography (80:100 hexane:acetone) to give a mixture of the *tetrahydrofurans* **433b** as a yellow oil (711 mg, 4.09 mmol, 61% over 2 steps from D-xylose, *d.r.* = 55:45).

Isolated as a yellow oil; R_f = 0.20 (1:1 acetone:hexane); ν_{max} (film/cm^{-1}) 3360s br. (O-H), 2875s (C-H), 1595s, 1470s, 1445s; ^{1}H NMR (600 MHz; D_2O) 6.92 (1H, d, *J* = 6.6, N=C*H* major), 6.88 (1H, d, *J* = 6.4, N=C*H* minor), 4.60 (1H, dd, *J* = 6.4, 3.6, N=CHC*H* minor), 4.40–4.38 (1H, m, C*H*CH$_2$ minor), 4.35–4.33 (2H, m, C*H*CH$_2$, N=CHC*H* major), 4.26–4.23 (2H, m, C*H*CHC*H*H' minor), 4.20–4.19 (1H, m, C*H*CHCH$_2$ major), 4.10 (1H, dd, *J* = 10.0, 4.1, C*H*H' major), 3.98 (1H, dd, *J* = 10.0, 2.0, CH*H*' major), 3.83 (1H, dd, *J* = 10.0, 1.1, CH*H*' minor), 2.80 (6H, s, N(C*H*$_3$)$_2$ minor), 2.78 (6H, s, N(C*H*$_3$)$_2$ major); ^{13}C NMR (150 MHz; D_2O, with a MeOH standard) 140.6 (*C*=N), 138.1 (*C*=N), 85.3 (*C*H), 81.0 (*C*H), 80.9 (*C*H), 78.1 (*C*H), 77.2 (*C*H), 77.1 (*C*H), 73.8 (*C*H$_2$), 73.7 (*C*H$_2$), 43.0 (N(*C*H$_3$)$_2$); HRMS (EI$^+$) found [M]$^+$ 174.0969; $C_7H_{14}N_2O_3$ requires 174.0999; $[\alpha]_D$ (20 °C) = +45.6 (MeOH, C = 1.1).

(2*R*,3*S*,4*R*)-2-((*E*)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (*ent-anti*-433b) and ((2*S*,3*S*,4*R*)-2-((*E*)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (*ent-syn*-433b)



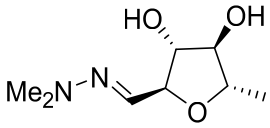
ent-anti-**443b**



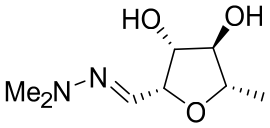
ent-syn-**433b**

Prepared according to the General Hydrazone Synthesis Procedure from L-xylose (1.00 g, 6.67 mmol) to give a crude hydrazone, which was subjected to the General Acid-Catalyzed Cyclization Procedure to give the crude product (*d.r.* = 55:45). This was purified by flash column chromatography (90:100 petroleum ether 40–60 °C:acetone) to give the *tetrahydrofuran ent*-**433b** as a yellow oil (656 mg, 3.77 mmol, 57% over 2 steps from L-xylose, *d.r.* = 55:45); ^{1}H NMR consistent with **443b**; $[\alpha]_D$ (20 °C) = –45.3 (MeOH C = 1.2).

(2*S*,3*R*,4*R*,5*S*)-2-((*E*)-(2,2-Dimethylhydrazono)methyl)-5-methyltetrahydrofuran-3,4-diol (*anti*-433c) and (2*R*,3*R*,4*R*,5*S*)-2-((*E*)-(2,2-Dimethylhydrazono)methyl)-5-methyltetrahydrofuran-3,4-diol (*syn*-433c)



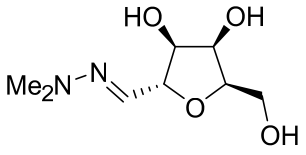
anti-**433c**



syn-**433c**

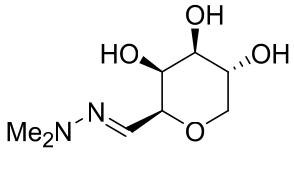
Prepared from hydrazone **431e** (1.37 g, 6.65 mmol) according General Acid-Catalyzed Cyclization Procedure to give the crude product (*d.r.* = 60:40). This was purified by flash column chromatography (80:100 hexane:acetone) to give the *tetrahydrofuran* **433c** as a yellow oil (866 mg, 4.61 mmol, 69%, *d.r.* = 60:40); R_f = 0.38 (1:1 acetone:hexane); ν_{max} (film/cm^{-1}) 3377s br. (O-H), 2921s (C-H), 1642s, 1445s; ^{1}H NMR (600 MHz; MeOH-d$_4$) 6.64 (1H, d, *J* = 7.0, N=C*H* minor), 6.61 (1H, d, *J* = 6.4, N=C*H* major), 4.41 (1H, dd, *J* = 7.0, 4.6, N=CHC*H* minor), 4.25 (1H, t, *J* = 6.4, N=CHC*H* major), 4.03 (1H, t, *J* = 6.4, N=CHCHC*H* major), 4.01–3.98 (1H, m, N=CHCHC*H* minor), 3.88 (1H, quintet, *J* = 6.4, C*H*CH$_3$ major), 3.79–3.74 (2H, m, C*H*C*H*CH$_3$ minor), 3.69 (1H, t, *J* = 6.4, C*H*CHCH$_3$ major), 2.81 (6H, s, N(C*H*$_3$)$_2$ minor), 2.79 (6H, s, N(C*H*$_3$)$_2$ major), 1.34 (3H, d, *J* = 6.0, CHC*H*$_3$ minor), 1.28 (3H, d, *J* = 6.4, CHC*H*$_3$ major); ^{13}C NMR (150 MHz; MeOH-d$_4$) 136.1 (*C*=N major), 134.3 (*C*=N minor), 84.8 (*C*H minor), 84.1 (*C*H major), 83.7 (*C*H major), 82.7 (*C*H minor), 82.5 (*C*H minor), 81.8 (*C*H major), 80.9 (*C*H minor), 80.2 (*C*H major), 42.9 (N(*C*H$_3$)$_2$ major), 42.8 (N(*C*H$_3$)$_2$ minor), 19.6 (CH*C*H$_3$ minor), 19.3 (CH*C*H$_3$ major); HRMS (ESI$^+$) found [M+H]$^+$ 189.1235; $C_8H_{17}N_2O_3$ requires 189.1239; $[\alpha]_D$ (20 °C) = –33.2 (MeOH, C = 3.3).

(2*R*,3*S*,4*R*,5*R*)-2-((*E*)-(2,2-Dimethylhydrazono)methyl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (443d) and (2*S*,3*S*,4*S*,5*R*)-2-((*E*)-(2,2-Dimethylhydrazono)methyl)tetrahydro-2*H*-pyran-3,4,5-triol (448)



443d

+



448

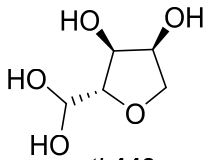
Prepared from hydrazone **441f** (222 mg, 1.00 mmol) according to the General Acid-Catalyzed Cyclization Procedure to give the crude product (**443d**:**448** = 60:40). This was

purified by flash column chromatography (30:70 hexane:acetone) to give the *tetrahydrofuran* **443d** as a colorless oil (59 mg, 0.29 mmol, 29%). Further elution of the column gave the *tetrahydropyran* **436** as a colorless oil (49 mg, 0.24 mmol, 24%, 20% impurity of **433d**).

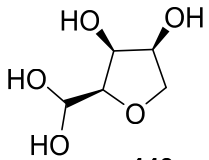
***Tetrahydrofuran* 443d:** R_f = 0.43 (70:30 acetone:hexane); ν_{max} (film/cm^{-1}) 3372s br. (O-H), 2898s (C-H), 1599w, 1444m, 1406m; ^{1}H NMR (600 MHz; D_2O) 6.93 (1H, d, *J* = 6.0, N=C*H*), 4.22 (1H, dd, *J* = 9.4, 6.0, N=CHC*H*), 4.15–4.12 (1H, m, C*H*CHCH$_2$), 4.04 (1H, dd, *J* = 9.4, 3.2, N=CHCHC*H*), 4.01–3.98 (2H, m, C*H*C*H*H'), 3.85–3.82 (1H, m, CH*H*'), 2.89 (6H, s, N(C*H*$_3$)$_2$); ^{13}C NMR (150 MHz; D_2O with MeOH standard) 139.0 (*C*=N), 75.8 (*C*H), 70.0 (*C*H), 69.8 (*C*H), 67.6 (*C*H), 66.7 (*C*H$_2$), 43.0 (N(*C*H$_3$)$_2$); HRMS (ES$^+$) found [M+H]$^+$ 205.1181; $C_8H_{17}N_2O_4$ requires 205.1188; $[\alpha]_D$ (20 °C) = +1.2 (MeOH, C = 0.5).

***Tetrahydropyran* 448:** Isolated with a 20% impurity of **443d**; R_f = 0.28 (1:1 acetone:hexane); ^{1}H NMR (600 MHz; D_2O) 6.97 (1H, d, *J* = 5.1, N=C*H*), 4.24 (1H, d, *J* = 5.1, N=CHC*H*), 4.16–4.11 (2H, m, C*H*H', N=CHCHC*H*), 3.98–3.94 (1H, m, C*H*CH$_2$), 3.74 (1H, dd, *J* = 9.6, 3.4, C*H*CHCH$_2$), 3.37 (1H, t, *J* = 10.9, CH*H*'), 2.86 (6H, s, N(C*H*$_3$)$_2$); ^{13}C NMR (150 MHz; D_2O with MeOH standard) 139.1 (*C*=N), 79.1 (*C*H), 74.4 (*C*H), 71.4 (*C*H), 69.6 (*C*H$_2$), 66.9 (*C*H), 43.1 (N(*C*H$_3$)$_2$).

(2*S*,3*S*,4*S*)-2-(Dihydroxymethyl)tetrahydrofuran-3,4-diol (*anti*-449a) and (2*R*,3*S*,4*S*)-2-(Dihydroxymethyl)tetrahydrofuran-3,4-diol (*syn*-449a)



anti-**449a**



syn-**449a**

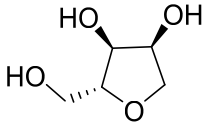
Amberlyst 15 (6.90 g) was added to as stirring solution of hydrazone **443a** (1.20 g, 6.90 mmol) in water (34 mL) at RT. After 5 minutes the reaction was filtered and concentrated *in vacuo* and lyophilized to give the hydrolyzed product as a white gum (894 mg); R_f = 0.42 (acetone); ν_{max} (film/cm^{-1}) 3345s br. (O-H), 2945s (C-H), 1720w, 1441m; $[\alpha]_D$ (20 °C) = +36.9 (MeOH, C = 1.0).

Analysis of the ^{1}H NMR in H_2O, D_2O, DMSO-d_6 and MeOH-d_4 suggested that the structure of the hydrolyzed product **449** was dependent on the solvent. In H_2O and D_2O

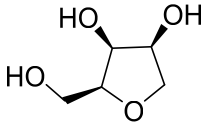
(accounting for deuterium exchange) the NMR data was consistent with a mixture of (2*S*,3*S*,4*S*)-2-(dihydroxymethyl)tetrahydrofuran-3,4-diol *anti*-**449a** and (2*R*,3*S*,4*S*)-2-(dihydroxymethyl)tetrahydrofuran-3,4-diol *syn*-**449a** (*anti*:*syn* = 85:15). In DMSO-d_6 and MeOH-d_4 the NMR data was consistent with a more complex composition [see **Section 4.2.5.** for further discussion].

(2*S*,3*S*,4*S*)-2-(Dihydroxymethyl)tetrahydrofuran-3,4-diol *anti*-449a and (2*R*,3*S*,4*S*)-2-(Dihydroxymethyl)tetrahydrofuran-3,4-diol *syn*-449a: ^{1}H NMR (600 MHz; D_2O) 5.16 (1H, d, *J* = 7.2, C*H*(OD)$_2$ *syn*-**449a**), 5.04 (1H, d, *J* = 5.1, C*H*(OD)$_2$ *anti*-**449a**), 4.49 (1H, td, *J* = 7.2, 4.0, C*H*CH$_2$ *syn*-**449a**), 4.31–4.27 (1H, m, C*H*CH$_2$ *anti*-**449a**; 1H, m, C*H*CHCH$_2$ *syn*-**449a**), 4.24 (1H, t, *J* = 5.1, C*H*CHCH$_2$ *anti*-**449a**), 4.06–4.02 (1H, dd, *J* = 10.0, 4.1, C*H*H' *anti*-**449a**; 1H, m, C*H*H' *syn*-**449a**), 3.82 (1H, dd, *J* = 10.0, 3.0, CH*H*' *anti*-**449a**), 3.79 (1H, dd, *J* = 7.2, 4.0, C*H*CH(OD)$_2$ *syn*-**449a**), 3.75 (1H, t, *J* = 5.1, C*H*CH(OD)$_2$ *anti*-**449a**), 3.71 (1H, t, *J* = 7.2, CH*H*' *syn*-**449a**); ^{13}C NMR (150 MHz; D_2O with MeOH standard) 90.4 (*C*H(OD)$_2$ *anti*-**449a**), 89.2 (*C*H(OD)$_2$ *syn*-**449a**), 84.2 (*C*HCH(OD)$_2$ *anti*-**449a**), 83.3 (*C*HCH(OD)$_2$ *syn*-**449a**), 73.0 (C*H*CH$_2$ *anti*-**449a**), 72.7 (O*C*H$_2$ *anti*-**449a**), 71.9 (*C*HCHCH$_2$ *anti*-**449a**), 71.8 (*C*HCH$_2$CH$_2$ *syn*-**449a**), 71.5 (*C*HCH$_2$ *syn*-**449a**), 70.8 (O*C*H$_2$ *syn*-**449a**).

(2*S*,3*R*,4*S*)-2-((*E*)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (*anti*-450)[251] and (2*R*,3*R*,4*S*)-2-((*E*)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuran-3,4-diol (*syn*-450)



anti-**450**

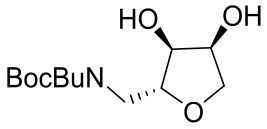


syn-**450**

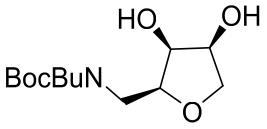
A stirring solution of hydrolyzed product **449** (103 mg, 0.780 mmol, *anti*:*syn* = 85:15) in MeOH (3.9 mL) was treated with $NaBH_4$ (43 mg, 1.2 mmol) portionwise at 0 °C. The reaction was stirred at 0 °C for 1 h before the reaction was quenched with AcOH (1 drop) and treated with Amberlyst 15 (1.60 g) and Amberlyst A26 (1.60 g). The mixture was then stirred at RT for 30 minutes before it was filtered the filtrate concentrated *in vacuo* to give the *triol* **450** as a white crystalline solid (104 mg, 0.776 mmol, 100%, *anti*:*syn* = 85:15); m.p. = 83–85 °C; R_f = 0.57 (acetone); ν_{max} (film/cm^{-1}) 3342s br. (O-H), 2930s (C-H), 1683w, 1411m; ^{1}H NMR (600 MHz; D_2O) 4.44 (1H, q, *J* = 5.8, C*H*CH$_2$

syn-**450**), 4.33 (1H, t, *J* = 4.8, C*H*CHCH$_2$ *syn*-**450**), 4.31–4.29 (1H, m, C*H*CH$_2$ *anti*-**450**), 4.13 (1H, dd, *J* = 7.3, 4.9, C*H*CHCH$_2$ *anti*-**450**), 4.09 (1H, dd, *J* = 10.2, 4.3, C*H*H' *anti*-**450**), 4.08–4.06 (1H, m, C*H*CH$_2$ *syn*-**450**), 3.99 (1H, dd, 9.2, 6.4, C*H*H' *syn*-**450**), 3.90–3.86 (1H, m, C*H*CH$_2$ *anti*-**450**), 3.85–3.81 (2H, m, C*H*H', CH*H*' *anti*-**450**; 1H, m, C*H*H' *syn*-**450**), 3.77–3.73 (2H, m, CH*H*', CH*H*' *syn*-**450**), 3.67 (1H, dd, *J* = 12.5, 5.1 CH*H*' *anti*-**450**); ^{13}C NMR (150 MHz; D_2O with MeOH reference) 82.1 (*C*H *anti*-**450**), 81.4 (*C*H *syn*-**450**), 72.8 (*C*H$_2$ *anti*-**450**), 72.2 (*C*H *anti*-**450**), 71.8 (*C*H *syn*-**450**), 71.7 (*C*H *syn*-**450**), 71.7 (*C*H *anti*-**450**), 71.0 (*C*H$_2$ *syn*-**450**), 61.9 (*C*H$_2$ *anti*-**450**), 61.0 (*C*H$_2$ *syn*-**450**); HRMS (CI$^+$) found $[M+H]^+$ 135.0652; $C_5H_{11}O_4$ requires 135.0652; $[\alpha]_D$ (20 °C) = +50.9 (MeOH, C = 2.0); data in accordance with the literature.[251]

tert-Butyl butyl(((2*R*,3*S*,4*S*)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)carbamate (*anti*-453) and _tert_-Butyl butyl(((2*S*,3*S*,4*S*)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)carbamate (*syn*-453)



anti-**453**

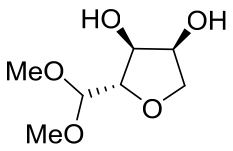


syn-**453**

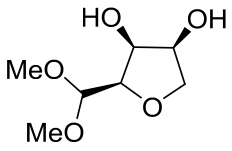
A stirring solution of hydrolyzed product **449** (124 mg, 0.939 mmol, *anti*:*syn* = 85:15) in MeOH (4.7 mL) was treated with AcOH (27 µL, 28 mg, 0.47 mmol), ^{n}BuNH$_2$ (0.47 mL, 640 mg, 8.7 mmol) and 10% Pd/C (124 mg) at RT before the reaction was placed under an atmosphere of hydrogen gas. The reaction was stirred at RT for 4 h before it was filtered through Celite and the filtrate concentrated *in vacuo*. The crude product was then dissolved in CPME (2.0 mL) and stirred at RT. The reaction was treated with a solution of Boc_2O (308 mg, 1.41 mmol) in CPME (3.0 mL) and resulting mixture stirred at RT for 16 h. The reaction was then concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (70:30 hexane:acetone) to give the *carbamate* **453** as a white gum (179 mg, 0.619 mmol, 66%, *anti*:*syn* = 80:20); R_f = 0.38 (30:70 acetone:hexane); ν_{max} (film/cm^{-1}) 3406s br. (O-H), 2931s (C-H), 1690s, 1665s, 1479s, 1468s, 1416s; ^{1}H NMR (400 MHz; DMSO-d_6, 80 °C) 4.90–4.06 (2H, br. m, 2 × O*H anti*-**453**; 3H, br. m, 2 × O*H syn*-**453**, C*H syn*-**453**), 4.05–4.00 (1H, m, C*H anti*-**453**), 3.94–3.88 (1H, m, *H syn*-**453**), 3.91 (1H, dd, *J* = 9.3, 5.3, C*H*H*' anti*-**453**), 3.88–3.83 (1H, m, C*H syn*-**453**), 3.76–3.70 (1H, m, C*H anti*-**453**, 1H, m, *H syn*-**453**), 3.66 (1H, dd, *J* = 6.0, 5.3, C*H anti*-**453**), 3.54–3.47 (2H, m, *H syn*-**453**), 3.51 (1H, dd, *J* = 9.3, 4.0, CH*H*' *anti*-

453), 3.44 (1H, dd, *J* = 14.3, 4.0, C*H*H' *anti*-**453**), 3.27–3.15 (2H, m, CH_2^nPr *anti*-**453**; 3H, m, CH_2^nPr *syn*-**453**, *H syn*-**453**), 3.11 (1H, dd, *J* = 14.3, 7.3, CH*H*' *anti*-**453**), 1.52–1.44 (2H, m, CH_2CH$_2$CH$_3$ *anti*-**453**; 2H, m, CH_2CH$_2$CH$_3$ *syn*-**453**), 1.42 (9H, s, C(CH_3)$_3$ *anti*-**453**), 1.41 (9H, s, C(CH_3)$_3$ *syn*-**453**), 1.31–1.21 (2H, m, CH_2CH$_3$ *anti*-**453**; 2H, m, CH_2CH$_3$ *syn*-**453**), 0.90 (3H, t, *J* = 7.3, CH$_2$CH_3 *anti*-**453**; 3H, t, *J* = 7.3, CH$_2$CH_3 *syn*-**453**); ^{13}C NMR (150 MHz; DMSO-d$_6$) 154.9 (*C*(O)), 154.6 (*C*(O)), 81.2 (*C*H), 80.8 (*C*H), 78.3 (*C*O^{t}Bu), 73.5 (*C*H), 72.2 (*C*H$_2$), 71.3 (*C*H), 70.9 (*C*H), 70.5 (*C*H$_2$), 70.1 (*C*H), 49.1 (*C*H$_2$), 48.8 (*C*H$_2$), 47.0 (*C*H$_2$), 46.5 (*C*H$_2$), 30.0 (*C*H$_2$), 29.5 (*C*H$_2$), 28.1 (C(*C*H$_3$)$_3$), 19.5 (*C*H$_2$), 13.8 (CH$_2$*C*H$_3$)); HRMS (ESI$^+$) found [M+H]$^+$ 290.1979; C$_{14}$H$_{28}$NO$_5$ requires 290.1967; [α]$_D$ (20 °C) = +25.0 (MeOH, C = 1.0).

(2*S*,3*S*,4*S*)-2-(Dimethoxymethyl)tetrahydrofuran-3,4-diol (*anti*-454) and (2*R*,3*S*,4*S*)-2-(Dimethoxymethyl)tetrahydrofuran-3,4-diol (*syn*-454)



anti-**454**

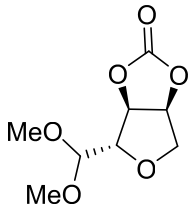


syn-**454**

Amberlyst 15 (83 mg) was added to a stirring solution of hydrolyzed product **449** (109 mg, 0.820 mmol, *anti*:*syn* = 85:15) in MeOH (4.1 mL) RT. The reaction was stirred at RT for 48 h before the reaction mixture was filtered and the filtrate concentrated *in vacuo* to give the crude product (*anti*:*syn* = 65:35). This was purified by flash column chromatography (80:100 hexane:acetone) to give the acetal-**454** as a colorless oil (111 mg, 0.624 mmol, 76%, *anti*:*syn* = 75:25); R_f = 0.34 (1:1 hexane:acetone); ν_{max} (film/cm^{-1}) 3443s br. (O-H), 2947s (C-H); ^{1}H NMR (600 MHz; MeOH-d$_4$) 4.59 (1H, d, *J* = 7.5, C*H*(OMe)$_2$ *syn*-**454**), 4.33–4.29 (1H, m, C*H*CH$_2$ *syn*-**454**), 4.31 (1H, d, *J* = 4.7, C*H*(OMe)$_2$ *anti*-**454**), 4.13 (1H, q, *J* = 4.7, C*H*CH$_2$ *anti*-**454**), 4.10–4.06 (1H, m, C*H*CHCH(OMe)$_2$ *syn*-**454**), 4.09 (1H, t, *J* = 4.7, C*H*CHCH(OMe)$_2$ *anti*-**454**), 3.93 (1H, dd, *J* = 9.2, 4.7, C*H*H' *anti*-**454**), 3.89 (1H, t, *J* = 7.9, C*H*H' *syn*-**454**), 3.83 (1H, t, *J* = 4.7, C*H*CH(OMe)$_2$ *anti*-**454**), 3.79 (1H, dd, *J* = 7.5, 3.4, C*H*CH(OMe)$_2$ *syn*-**454**), 3.68 (1H, dd, *J* = 9.2, 4.7, CH*H*' *anti*-**454**), 3.65 (1H, t, *J* = 7.9, CH*H*' *syn*-**454**), 3.44 (3H, s, OCH_3 *syn*-**454**), 3.43 (3H, s, OCH_3 *anti*-**454**), 3.42 (3H, s, OCH_3 *anti*-**454**), 3.39 (3H, s, OCH_3 *syn*-**454**); ^{13}C NMR (150 MHz; MeOH-d$_4$) 106.3 (*C*(OMe)$_2$ *anti*-**454**), 104.2 (*C*(OMe)$_2$ *syn*-**454**), 84.1 (*C*HCH(OMe)$_2$ *anti*-**454**), 81.5 (*C*HCH(OMe)$_2$ *syn*-**454**), 73.6 (*C*HCHCH$_2$

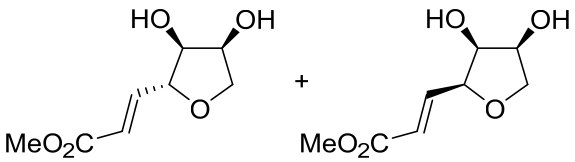
anti-**454**), 73.3 (*C*H_2O *anti*-**454**), 73.0 (*C*HO *syn*-**454**), 72.6 (*C*HCH$_2$ *anti*-**454**), 72.5 (*C*HO *syn*-**454**), 72.1 (*C*H_2O *syn*-**454**), 56.1 (O(*C*H_3)$_2$ *anti*-**454**), 55.2 (O(*C*H_3)$_2$ *syn*-**454**); HRMS (ESI$^+$) found [M+Na]$^+$ 201.0741; $C_7H_{14}NaO_5$ requires 201.0739; $[\alpha]_D$ (20 °C) = +30.1 (MeOH, C = 0.38).

(3a*S*,4*S*,6a*S*)-4-(Dimethoxymethyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-2-one (455)



K_2CO_3 (7 mg, 10 mol%) was added to a stirring solution of acetal **454** (90 mg, 0.51 mmol, *anti*:*syn* = 75:25) in DMC (2.5 mL) at RT. The reaction was heated at reflux for 16 h before the reaction was allowed to cool to RT, filtered through a silica plug (eluting with Et_2O) and the filtrate concentrated *in vacuo* to give the *carbonate* **455** as a colorless oil (90 mg, 0.44 mmol, 87%, single diastereoisomer); R_f = 0.35 (80:20 hexane:acetone); ν_{max} (film/cm^{-1}); 2942s (C-H), 1797s (C=O), 1459s; ^{1}H NMR (600 MHz; $CDCl_3$) 5.26 (1H, d, *J* = 7.0, C*H*CHCH$_2$), 5.18–5.16 (1H, m, C*H*CH$_2$), 4.33 (1H, d, *J* = 2.7, C*H*(OMe)$_2$), 4.25 (1H, d, *J* = 2.7, C*H*CH(OMe)$_2$), 4.14–4.12 (2H, m, OC*H*$_2$), 3.46 (3H, s, OC*H*$_3$), 2.43 (3H, s, OC*H*$_3$); ^{13}C NMR (150 MHz; $CDCl_3$) 154.5 (*C*(O)), 105.6 (*C*(OMe)$_2$), 84.0 (*C*HCH(OMe)$_2$), 81.3 (*C*HCHCH$_2$), 80.9 (*C*HCH$_2$), 73.9 (O*C*H$_2$), 56.9 (O*C*H$_3$), 56.5 (O*C*H$_3$); HRMS (CI$^+$) found [M+H]$^+$ 205.0708; $C_8H_{13}O_6$ requires 205.0707; $[\alpha]_D$ (20 °C) = +25.0 (MeOH, C = 0.45).

Methyl (*E*)-3-((2*R*,3*S*,4*S*)-3,4-dihydroxytetrahydrofuran-2-yl)acrylate (*anti*-456) and Methyl (*E*)-3-((2*S*,3*S*,4*S*)-3,4-dihydroxytetrahydrofuran-2-yl)acrylate (*syn*-456)

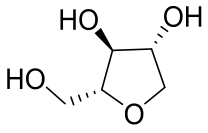


anti-**456** *syn*-**456**

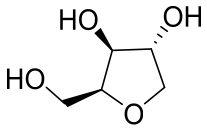
K_2CO_3 (78 mg, 0.57 mmol) and trimethyl phosphonoacetate (74 μL, 82 mg, 0.43 mmol) were added to a stirring solution of hydrolyzed product **449** (50 mg, 0.38 mmol, *anti*:*syn* = 85:15) in MeOH (1.9 mL) at 0 °C. The reaction was stirred at 0 °C for 4 h before the

reaction mixture was filtered through a silica plug (eluting with EtOAc) and the filtrate concentrated *in vacuo* to give the crude product (*anti*:*syn* = 85:15). This was purified by flash column chromatography (CH_2Cl_2) to give the *alkene* **456** as a colorless oil (53 mg, 0.28 mmol, 74%, *anti*:*syn* = 85:15); R_f = 0.58 (1:1 acetone:hexane); ν_{max} (film/cm^{-1}) 3400s br. (O-H), 2944s (C-H), 1715s (C=O), 1649s, 1319s; ^{1}H NMR (600 MHz; MeOH-d_4) 7.02 (1H, dd, *J* = 15.6, 4.7, MeO_2CCH=C*H syn*-**456**), 6.98 (1H, dd, *J* = 15.8, 6.3, MeO_2CCH=C*H anti*-**456**), 6.08 (1H, dd, *J* = 15.8, 1.7, MeO_2CCH *anti*-**456**), 6.07–6.04 (1H, m, MeO_2CCH *syn*-**456**), 4.50 (1H, td, *J* = 4.7, 1.7, CH=CHC*H syn*-**456**), 4.34–4.31 (1H, m, C*H*CH_2 *syn*-**456**), 4.30–4.27 (1H, m, CH=CHC*H anti*-**456**), 4.19 (1H, t, *J* = 4.7, C*H*$CHCH_2$ *syn*-**456**), 4.18–4.15 (1H, m, CH_2CH *anti*-**456**), 4.12 (1H, dd, *J* = 9.8, 4.5, C*H*H' *anti*-**456**), 3.96–3.93 (1H, m, C*H*H' *syn*-**456**), 3.88–3.78 (2H, m, CH*H*'CHC*H anti*-**456**), 3.76–3.74 (1H, m, CH*H*' *syn*-**456**), 3.73 (3H, s, OCH_3 *anti*-**456**), 3.72 (3H, s, OCH_3 *syn*-**456**); ^{13}C NMR (150 MHz; MeOH-d_4) 168.3 (*C*(O), *anti*-**456**; *C*(O), *syn*-**456**), 148.1 (MeO_2CCH=*C*H *anti*-**456**), 146.7 (MeO_2CCH=*C*H *syn*-**456**), 122.5 (MeO_2CC*C*H=CH *syn*-**456**), 121.5 (MeO_2CC*C*H=CH *anti*-**456**), 81.6 (CH=CH*C*H *syn*-**456**), 81.5 (CH=CH*C*H *anti*-**456**), 77.7 (CH_2CHC*C*H *anti*-**456**), 74.3 (*C*H_2 *anti*-**456**), 74.2 (*C*HOD *syn*-**456**), 73.1 (*C*HOD *syn*-**456**), 72.6 (*C*H_2 *syn*-**456**), 72.4 (CH_2*C*H *anti*-**456**), 52.1 (OCH_3 *anti*-**456**), 52.1 (OCH_3 *syn*-**456**); HRMS (EI^+) found $[M]^+$ 188.0680; $C_8H_{12}O_5$ requires 188.0679; $[\alpha]_D$ (20 °C) = +40.5 (MeOH, C = 0.45).

(2*R*,3*S*,4*R*)-2-(Hydroxymethyl)tetrahydrofuran-3,4-diol (*anti*-458)[252] and (2*S*,3*S*,4*R*)-2-(Hydroxymethyl)tetrahydrofuran-3,4-diol (*syn*-458)



anti-**458**

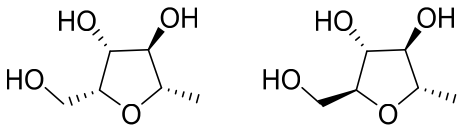


syn-**458**

Amberlyst 15 (701 mg) was added to a stirring solution of hydrazone **443b** (122 mg, 0.701 mmol, 55:45 *d.r.*) in water (3.5 mL) at RT. After 5 minutes the reaction mixture was filtered and the filtrate concentrated *in vacuo* and lyophilized to give a white gum. The intermediate was then dissolved in MeOH (3.5 mL) and treated with $NaBH_4$ (40 mg, 1.1 mmol) portionwise at 0 °C and the reaction stirred at 0 °C for 1 h. The reaction was then quenched with AcOH (1 drop) and treated with Amberlyst 15 (1.4 0g) and Amberlyst A26 (1.40 g). The mixture was then stirred at RT for 30 minutes before it was filtered the filtrate concentrated *in vacuo* to give *triol* **458** as a colorless oil (85 mg, 0.63 mmol, 90%,

anti:*syn* = 65:35); R_f = 0.57 (acetone); ν_{max} (film/cm^{-1}) 3330s br. (O-H), 2939s (C-H), 1655m, 1414s; ^{1}H NMR (600 MHz; D_2O) 4.33–4.29 (1H, m, C*H syn*-**458**), 4.27–4.25 (1H, m, C*H anti*-**458**), 4.23 (1H, dd, *J* = 3.6, 1.3, C*H syn*-**458**), 4.18 (1H, dd, *J* = 10.3, 4.2, C*H*H' *syn*-**458**), 4.16–4.12 (1H, m, C*H syn*-**458**), 4.05–4.02 (2H, m, C*H*, C*H*H' *anti*-**458**), 3.89–3.84 (2H, m, C*H,* CH*H' anti*-**458**; 1H, m, C*H*H' *syn*-**458**), 3.80–3.71 (2H, m, CH_2 *anti*-**458**; 2H, m, CH*H*', CH*H*' *syn*-**458**); ^{13}C NMR (150 MHz; D_2O with MeOH standard) 86.1 (*C*H *anti*-**458**), 81.4 (*C*H *syn*-**458**), 78.5 (*C*H *anti*-**458**), 77.5 (*C*H *anti*-**458**), 77.2 (*C*H *syn*-**458**), 76.7 (*C*H *syn*-**458**), 73.4 (*C*H_2 *anti*-**458**), 73.3 (*C*H_2 *syn*-**458**), 62.2 (*C*H_2 *anti*-**458**), 60.5 (*C*H_2 *syn*-**458**); HRMS (ESI$^+$) found $[M+H]^+$ 135.0658; $C_5H_{11}O_4$ requires 135.0652; $[\alpha]_D$ (20 °C) = +69.6 (MeOH, C = 0.17); Data for *anti*-**458** in accordance with the literature.[252]

(2*R*,3*R*,4*R*,5*S*)-2-(Hydroxymethyl)-5-methyltetrahydrofuran-3,4-diol (*syn*-459)[253] and (2*S*,3*R*,4*R*,5*S*)-2-(Hydroxymethyl)-5-methyltetrahydrofuran-3,4-diol (*anti*-459)

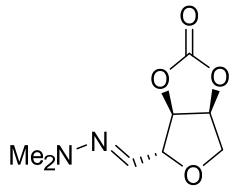


syn-**459** *anti*-**459**

Amberlyst 15 (888 mg) was added to a stirring solution of hydrazone **433c** (167 mg, 0.888 mmol, 60:40 *d.r.*) in water (4.4 mL) at RT. After 5 minutes the reaction mixture was filtered and the filtrate concentrated *in vacuo* and lyophilized to give a white gum. The intermediate was then dissolved in MeOH (4.4 mL) and treated with $NaBH_4$ (49 mg, 1.3 mmol) portionwise at 0 °C and the reaction stirred at 0 °C for 1 h. The reaction was then quenched with AcOH (1 drop) and treated with Amberlyst 15 (1.80 g) and Amberlyst A26 (1.80 g). The mixture was then stirred at RT for 30 minutes before it was filtered and the filtrate concentrated *in vacuo* to give the *triol* **459** as a colorless oil (122 mg, 0.824 mmol, 93%, *syn*:*anti* = 70:30); R_f = 0.26 (1:1 acetone:hexane); ν_{max} (film/cm^{-1}) 3317s (O-H), 2930s (C-H), 1450s; ^{1}H NMR (600 MHz; D_2O) 4.21–4.19 (1H, m, C*H anti*-**459**), 4.09–4.06 (1H, m, C*H anti*-**459**), 4.04 (1H, t, *J* = 6.4, C*H*OD *syn*-**459**), 3.96–3.91 (2H, m, C*H*CH_2, C*H*CH_3 *syn*-**459**), 3.86–3.80 (1H, m, C*H*OD *syn*-**459**; 3H, m, C*H*CH_3, C*H*H', C*H anti*-**459**), 3.78–3.73 (1H, m, C*H*H' *syn*-**459**; 1H, m, C*H*H' *anti*-**459**), 3.72–3.69 (1H, dd, *J* = 12.4, 5.8, CH*H syn*-**459**), 1.37–1.35 (3H, m, CHCH_3 *anti*-**459**), 1.32 (3H, d, *J* = 6.4, CHCH_3 *syn*-**459**); ^{13}C NMR (150 MHz; D_2O with MeOH standard) 83.4

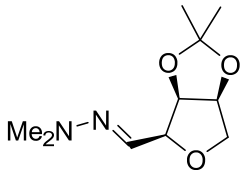
(*C*H *anti*-**459**), 82.5 (*C*H *syn*-**459**), 82.3 (*C*H *syn*-**459**), 81.3 (*C*H *anti*-**459**), 80.9 (*C*H *anti*-**459**), 78.6 (*C*H *syn*-**459**), 78.2 (*C*H *anti*-**459**), 77.2 (*C*H *syn*-**459**), 61.9 (CH_2 *syn*-**459**), 60.7 (CH_2 *anti*-**459**), 18.7 (CH_3 *anti*-**459**), 18.3 (CH_3 *syn*-**459**); HRMS (CI^+) found $[M+H]^+$ 149.0821; $C_6H_{13}O_4$ requires 149.0808; $[\alpha]_D$ (20 °C) = –28.7 (MeOH, C = 3.3); Data for *syn*-**459** accordance with the literature.[253]

(3a*R*,4*R*,6a*S*)-4-((*E*)-(2,2-Dimethylhydrazono)methyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-2-one (467)

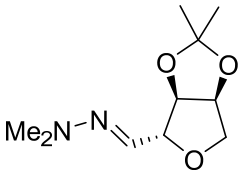


A solution of tetrahydrofuran *anti*-**433a** (316 mg, 1.82 mmol) in DMC (9.1 mL) was treated with K_2CO_3 (25 mg, 10 mol%) and the reaction mixture heated at reflux for 16 h. The reaction mixture was then allowed to cool to RT before it was filtered through a silica plug (elution with Et_2O) and the filtrate concentrated *in vacuo* to give the *carbonate* **467** as a colorless oil (364 mg, 1.82 mmol, 100%); R_f = 0.71 (1:1 acetone:hexane); ν_{max} (film/cm^{-1}) 2863m (C-H), 1798s (C=O), 1587s, 1468s, 1444s; ^{1}H NMR (600 MHz; $CDCl_3$) 6.35 (1H, d, *J* = 2.6, N=C*H*), 5.63 (1H, d, *J* = 6.8, C*H*CHCH$_2$), 5.18 (1H, d, *J* = 6.8, 3.8, C*H*CH$_2$), 4.90 (1H, d, *J* = 2.6, N=CHC*H*), 4.12 (1H, d, *J* = 11.5, C*H*H'), 3.76 (1H, dd, *J* = 11.5, 3.8, CH*H*'), 2.82 (6H, s, N(CH_3)$_2$); ^{13}C NMR (150 MHz; $CDCl_3$) 154.8 (*C*(O)), 127.0 (N=*C*H), 82.2 (N=CHC*H*), 81.4 (*C*HCHCH$_2$), 80.9 (C*H*CH$_2$), 70.5 (C*H*$_2$O), 42.5 (N(*C*H$_3$)$_2$); HRMS (EI^+) found $[M]^+$ 200.0796; $C_8H_{12}N_2O_4$ requires 200.0792; $[\alpha]_D$ (20 °C) = +122.2 (MeOH, C = 1.0).

(*E*)-2-(((3a*R*,4*S*,6a*S*)-2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methylene)-1,1-dimethylhydrazine (*syn*-442) and (*E*)-2-(((3a*R*,4*R*,6a*S*)-2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methylene)-1,1-dimethylhydrazine (*anti*-442)[245]



syn-**442**



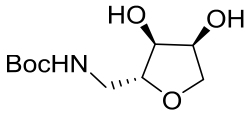
anti-**442**

A stirring solution of tetrahydrofuran *anti*-**443a** (154 mg, 0.885 mmol) in acetone (4.4 mL) was treated with $(MeO)_2CMe_2$ (0.89 mL) and PTSA.H_2O (34 mg, 0.18 mmol, 20 mol%) at RT and the reaction stirred at RT for 24 h. The reaction was then quenched with aq. sat. $NaHCO_3$ and filtered through a silica plug, eluting with acetone. The filtrate was concentrated *in vacuo* to give acetonide **442** as a colorless oil (182 mg, 0.850 mmol, 96%, *syn*:*anti* = 60:40); R_f = 0.45 and 0.35 (1:4 acetone:hexane); ν_{max} (film/cm^{-1}) 2934s (C-H), 1689s, 1597s, 1470s; HRMS (ESI^+) found $[M+H]^+$ 215.1398; $C_{10}H_{19}N_2O_3$ requires 215.1396; $[\alpha]_D$ (20 °C) = +103.0 (MeOH, C = 1.0); data in accordance with the literature.[245]

Acetonide *syn*-442: ^{1}H NMR (600 MHz; MeOH-d_4) 6.57 (1H, d, *J* = 6.8, N=C*H*), 4.86–4.82 (1H, m, C*H*CH_2), 4.71–4.66 (1H, m, C*H*$CHCH_2$), 4.00 (1H, dd, *J* = 6.8, 3.9, N=CHC*H*), 3.94 (1H, d, *J* = 10.5, OC*H*H'), 3.53 (dd, *J* = 10.5, 3.7, OCH*H*'), 2.81 (6H, s, N(CH_3)$_2$), 1.46 (3H, s, C(CH_3)), 1.31 (3H, s, C(CH_3)); ^{13}C NMR (150 MHz; MeOH-d_4) 132.1 (*C*=N), 113.2 (*C*(CH_3)$_2$), 83.7 (N=CH*C*H), 83.3 (*C*H$CHCH_2$), 82.7 (*C*HCH_2), 73.6 (OCH_2), 42.8 (N(*C*H_3)$_2$), 26.3 (C*C*H_3), 24.7 (C*C*H_3); data in accordance with the literature.[245]

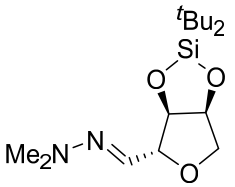
Acetonide *anti*-442: ^{1}H NMR (600 MHz; MeOH-d_4) 6.50 (1H, d, *J* = 4.3, N=C*H*), 4.97 (1H, d, *J* = 6.0, C*H*$CHCH_2$), 4.81 (1H, dd, *J* = 6.0, 4.3, C*H*CH_2), 4.54 (1H, d, *J* = 4.3, N=CHC*H*), 3.86 (1H, d, *J* = 10.5, C*H*H'), 3.75 (1H, d, *J* = 10.5, 4.3, CH*H*'), 2.77 (6H, s, N(CH_3)$_2$), 1.46 (3H, s, C(CH_3)), 1.32 (3H, s, C(CH_3)); ^{13}C NMR (150 MHz; MeOH-d_4) 132.5 (*C*=N), 113.4 (*C*(CH_3)$_2$), 85.1 (*C*H), 84.4 (*C*H), 82.4 (*C*H), 73.0 (OCH_2), 42.8 (N(*C*H_3)$_2$), 26.7 (C*C*H_3), 25.0 (C*C*H_3); data in accordance with the literature.[245]

***tert*-Butyl (((2*R*,3*S*,4*S*)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)carbamate (469)**



A stirring solution of tetrahydrofuran *anti*-**443a** (100 mg, 0.57 mmol) in CPME (2.9 mL) was treated with a solution of Boc_2O (313 mg, 1.44 mmol) in CPME (2.9 mL) at RT. The resulting solution was then treated with $Pd(OH)_2$ (20% on carbon, 163 mg) and the reaction was placed under an atmosphere of hydrogen gas (1 atm). The reaction was stirred at RT for 24 h before it was filtered through Celite and the filtrate concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (100:90 hexane:acetone) to give *carbamate* **469** as a colorless oil (80 mg, 0.34 mmol, 60%); R_f = 0.40 (100:90 hexane:acetone); ν_{max} (film/cm^{-1}) 3362s br. (O-H, N-H), 2977s (C-H), 1688s (C=O), 1523s, 1367s, 1251s; ^{1}H NMR (600 MHz; $CDCl_3$) 5.21–5.17 (1H, m, N*H*), 4.22–4.19 (1H, m, OCH_2CH), 4.05 (1H, dd, *J* = 10.2, 4.9, OC*H*H'), 3.84–3.80 (1H, m, NCH_2CHCH), 3.78–3.75 (2H, m, OCH*H*', NCH_2CH), 3.42–3.36 (1H, m, NC*H*H'), 3.31–3.26 (1H, m, NCH*H*'), 1.41 (9H, s, $C(CH_3)_3$); ^{13}C NMR (150 MHz; $CDCl_3$) 157.0 (*C*(O)), 80.6 (NCH_2CH), 80.2 (CMe_3), 73.2 (OCH_2), 73.1 (NCH_2CHCH), 71.2 (OCH_2CH), 42.0 (NCH_2), 28.5 ($C(CH_3)_3$); HRMS (ES$^+$) found $[M+H]^+$ 234.1339; $C_{10}H_{20}NO_5$ requires 234.1341; $[\alpha]_D$ (20 °C) = +32.9 (MeOH, C = 1.0).

(*E*)-2-(((3a*R*,4*R*,6a*S*)-2,2-Di-*tert*-butyltetrahydrofuro[3,4-*d*][1,3,2]dioxasilol-4-yl)methylene)-1,1-dimethylhydrazine (474)



A solution of tetrahydrofuran *anti*-**443a** (312 mg, 1.79 mmol) in DMC (18 mL) at 0 °C was treated with 2,6-lutidine (0.63 mL, 580 mg, 5.4 mmol) and di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (0.64 mL, 870 mg, 2.0 mmol). The resulting mixture was stirred at 0 °C for 1 h before the reaction was quenched with water (1 drop) and filtered through a silica plug, eluting with Et_2O. The filtrate was concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (10:90 EtOAc:hexane) to give *silyl ether* **474** as a colorless oil (269 mg, 0.857 mmol, 48%); R_f = 0.44 (20:80 EtOAc:hexane); ν_{max} (film/cm^{-1}) 2930s (C-H), 2856s (C-H), 1594w,

1472s; ^{1}H NMR (600 MHz; $CDCl_3$) 6.44 (1H, d, *J* = 4.0, N=C*H*), 4.87 (1H, dd, *J* = 6.6, 2.6, C*H*CHCH$_2$), 4.75–4.70 (1H, m, C*H*CH$_2$), 4.51–5.49 (1H, m, N=CHC*H*), 3.94 (1H, dd, *J* = 10.4, 5.3, C*H*H'), 3.84 (1H, dd, *J* = 10.4, 3.0, CH*H*'), 2.80 (6H, s, N(C*H*$_3$)$_2$), 1.09 (9H, s, C(C*H*$_3$)$_3$), 1.04 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz; $CDCl_3$) 131.3 (*C*=N), 85.2 (*C*H), 81.4 (*C*H), 79.3 (*C*H), 73.9 (*C*H$_2$), 42.7 (N(*C*H$_3$)$_2$), 27.4 (C(*C*H$_3$)$_3$), 26.9 (C(*C*H$_3$)$_3$), 21.9 (*C*(CH$_3$)$_3$), 20.1 (*C*(CH$_3$)$_3$); HRMS (EI$^+$) found $[M]^+$ 314.2022; $C_{15}H_{30}N_2O_3Si$ requires 314.2020; $[\alpha]_D$ (20 °C) = +78.0 (MeOH, C = 1.0).

6.4. Crystallography Data

All the information in the section was provided by Dr Dejan-Krešimir Bučar and Dr Laure Benhamou.

General Experimental Procedure: Single X-ray diffraction data were collected using an *Agilent SuperNova (Dual Source)* single crystal X-ray diffractometer equipped with an *Atlas CCD Detector*. The diffraction experiment was conducted at 150 K using CuK_α radiation (λ = 1.54184 Å). Data collection and processing was accomplished using the *CrysAlisPro* program.[285] Empirical absorption correction was performed using spherical harmonics implemented in the *SCALE3 ABSPACK* scaling algorithm.[285] Structure solution and refinement were accomplished using *SHELXS-97* and *SHELXL-97*, respectively.[286] The structure was solved using direct methods. All non-hydrogen atoms were refined anisotropically, while hydrogen atoms associated with carbon and oxygen atoms were refined isotropically in geometrically constrained positions.

Table A. General and crystallographic data for *endo*-**330e**.

Empirical formula	$C_{17}H_{17}NO_4$
Formula weight / g mol^{-1}	299.32
Temperature / K	150.00(10)
Crystal system	triclinic
Space group	$P\bar{1}$
***a* / Å**	7.2630(2)
***b* / Å**	10.8264(3)
***c* / Å**	19.9792(4)
***α* / °**	78.833(2)
***β* / °**	89.832(2)
***γ* / °**	71.899(2)
Volume / Å^3	1462.22(6)
Z	4
ρ_{calc}/ g cm^{-3}	1.36
μ / mm^{-1}	0.801
***F*(000)**	632.0
Crystal size / mm^3	0.41 × 0.17 × 0.07
Radiation	CuK_α (λ = 1.5418 Å)
2θ range for data collection / °	8.78 to 133.2
Index ranges	$-8 \leq h \leq 8$, $-12 \leq k \leq 12$, $-23 \leq l \leq 23$
Reflections collected	22496
Independent reflections	5146 [R_{int} = 0.0363, R_{sigma} = 0.0235]
Data / restraints / parameters	5146 / 0 / 400
Goodness-of-fit on F^2	0.998
Final *R* indexes [I ≥ 2σ(*I*)]	R_1 = 0.0393, wR_2 = 0.0975
Final *R* indexes [all data]	R_1 = 0.0453, wR_2 = 0.1016
Largest diff. peak/hole / e Å^{-3}	0.23 / –0.20
CCDC deposition number	1035038

Table B. General and crystallographic data for *exo*-**330e**.

Empirical formula	$C_{17}H_{17}NO_4$
Formula weight / g mol^{-1}	299.32
Temperature / K	150.00(10)
Crystal system	monoclinic
Space group	$P2_1/c$
***a* / Å**	6.64710(10)
***b* /Å**	14.1775(2)
***c* /Å**	15.4276(2)
***α* /°**	90
***β* /°**	97.1400(10)
***γ* /°**	90
Volume / Å^3	1442.61(4)
Z	4
ρ_{calc} / g cm^{-3}	1.378
***μ* / mm^{-1}**	0.812
***F*(000)**	632.0
Crystal size / mm^3	0.26 × 0.15 × 0.09
Radiation	CuK_α (λ = 1.5418 Å)
2*θ* range for data collection / °	8.5 to 133.18
Index ranges	$-7 \leq h \leq 7$, $-16 \leq k \leq 16$, $-18 \leq l \leq 18$
Reflections collected	20945
Independent reflections	2532 [R_{int} = 0.0455, R_{sigma} = 0.0194]
Data / restraints / parameters	2532 / 0 / 201
Goodness-of-fit on F^2	1.063
Final *R* indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0372, wR_2 = 0.0976
Final *R* indexes [all data]	R_1 = 0.0402, wR_2 = 0.1007
Largest diff. peak/hole / e Å^{-3}	0.24 / –0.19
CCDC deposition number	1035039

Table C. General and crystallographic data for *anti*-**443a**.

Empirical formula	$C_7H_{14}N_2O_3$
Formula weight / g mol^{-1}	174.2
Temperature / K	150.00(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a / Å	5.08850(10)
b / Å	17.8742(3)
c / Å	19.7947(3)
α / °	90
β / °	90
γ / °	90
Volume / Å^3	1800.38(5)
Z	8
ρ_{calc}/ g cm^{-3}	1.285
μ / mm^{-1}	0.843
F(000)	752
Crystal size / mm^3	0.31 × 0.04 × 0.03
Radiation	CuK_α (λ = 1.5418 Å)
Index ranges	$-3 \leq h \leq 6$, $-21 \leq k \leq 16$, $-23 \leq l \leq 17$
Reflections collected	4258
Unique reflections	2812
R_{int}	0.0197
Reflections with $I \geq 2\sigma(I)$	2639
Number of parameters	233
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0281, wR_2 = 0.0659
Final R indexes [all data]	R_1 = 0.0309, wR_2 = 0.0677
Largest diff. peak/hole / e Å^{-3}	0.160 / -0.138
CCDC deposition number	1411520

Chapter VII. References

[1] C. Jiménez-González, D. J. C. Constable, C. S. Ponder, *Chem. Soc. Rev*. **2012**, *41*, 1485–1498.

[2] W. J. W. Watson, *Green Chem*. **2012**, *14*, 251–259.

[3] http://www.gsk.com/en-gb/responsibility/our-planet/carbon/

[4] M. C. Bryan, B. Dillon, L. G. Hamann, G. J. Hughes, M. E. Kopach, E. A. Peterson, M. Pourashraf, I. Raheem, P. Richardson, D. Richter, H. F. Sneddon*, J. Med. Chem*. **2013**, *56*, 6007–6021.

[5] P. T. Anastas, J. C. Warner, Green Chemistry: Theory and Practice, Oxford University Press: New York, **1998**, p.30.

[6] N. Winterton, *Green Chem*. **2001**, *3*, G73–G81.

[7] P. T. Anastas and J. B. Zimmerman, in Sustainability Science and Engineering Defining Principles, ed. M. A. Abrahams, Elsevier, **2006**, pp. 11–32.

[8] S. L. Y. Tang, R. L. Smith, M. Poliakoff, *Green Chem*. **2005**, *7*, 761–762.

[9] R. A. Sheldon*, Chem. Ind. (London)*, **1992**, 903–906.

[10] R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273–1283.

[11] B. M. Trost, *Science* **1991**, *254*, 1471−1477.

[12] D. J. C. Constable, A. D. Curzons, V. L. Cunningham, *Green Chem.* **2002**, *4*, 521−527.

[13] C Jimenez-Gonzalez, C. S. Ponder, Q. B. Broxterman, J. B. Manley, *Org. Process Res. Dev.* **2011**, *15*, 912–917.

[14] A. D. Curzons, D. J. C. Constable, D. N. Mortimer, V. L. Cunningham, *Green Chem.* **2001**, *3*, 1−6.

[15] F. I. McGonagle, H. F. Sneddon, C. Jamieson, A. J. B. Watson, *ACS Sustainable Chem. Eng*. **2014**, *2*, 523−532.

[16] D. J. C. Constable, C. Jimenez-Gonzalez, R. K. Henderson, *Org. Process Res. Dev.* **2007**, *11*, 133–137.

[17] M. –O. Simona, C. –J. Li, *Chem. Soc. Rev.* **2012**, *41*, 1415–1427.

[18] P. G. Jessop, *Green Chem.* **2011**, *13*, 1391–1398.

[19] C. Capello, U. Fischer, K. Hungerbuhler, *Green Chem.* **2007**, *9*, 927–934.

[20] Regulation (EC) no. 1005/2009 of the European Parliament and of the Council of 16 September 2009.

[21] Guidance for Industry Q3C-Tables and List, Feb 2012, Revision 2, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073395.pdf

[22] D. Prat, J. Hayler, A. Wells*, Green Chem*. **2014**, *16*, 4546–4551.

[23] R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, A. D. Curzons, *Green Chem*. **2011**, *13*, 854–862.

[24]http://www.acs.org/content/dam/acsorg/greenchemistry/industriainnovation/roundtable/solvent-selection-guide.pdf

[25] K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry, M. Stefaniak, *Green Chem*. **2008**, *10*, 31–36.

[26] D. Prat, O. Pardigon, H. –W. Flemming, S. Letestu, V. Ducandas, P. Isnard, E. Guntrum, T. Senac, S. Ruisseau, P. Cruciani, P. Hosek, *Org. Process Res. Dev*. **2013**, *17*, 1517−1525.

[27]http://www.acs.org/content/dam/acsorg/greenchemistry/industriainnovation/roundtable/acs-gci-pr-solvent-selection-guide.pdf

[28] a) Reductive Amination: F. I. McGonagle, D. S. MacMillan, J. Murray, H. F. Sneddon, C. Jamieson, A. J. B. Watson, *Green Chem*. **2013**, *15*, 1159–1165; b) Amidation: D. S. MacMillan, J. Murray, H. F. Sneddon, C. Jamieson, A. J. B. Watson, *Green Chem*. **2013**, *15*, 596–600; c) Olefin Metathesis: K. Skowerski, J. Białecki, A. Tracza, T. K. Olszewski, *Green Chem*. **2014**, *16*, 1125–1130.

[29]a) V. Pace, P. Hoyos, M Fernandez, J. V. Sinisterrá, A. R. Alćantara, *Green Chem*, **2010**, *12*, 1380–1382; b) S. D. Ramgren, L. Hie, Y. Ye, N. K. Garg, *Org. Lett.* **2003**, *15,* 3950–3953.

[30] K. Watanabe, *Molecules* **2013**, *18*, 3183–3194.

[31] H. Bilel, N. Hamdi, F. Zagrouba, C. Fischmeister, C. Bruneau, *Green Chem*. **2011**, *13*, 1448–1452.

[32] B. Pieber, C. O. Kappe, *Green Chem*. **2013**, *15*, 320–324.

[33] a) G. Strappaveccia, E. Ismalaj, C. Petrucci, D. Lanari, A. Marrocchi, M. Drees, A. Facchetti, L. Vaccaro, *Green Chem*. **2015**, *17*, 365–372; b) G. Strappaveccia, L. Luciani, E. Bartollini, A. Marrocchi, F. Pizzo, L. Vaccaro, *Green Chem*. **2015**, *17*, 1071–1076.

[34] J. I. García, H. García-Marín, E. Pires, *Green Chem*. **2014**, *16*, 1007–1033.

[35] S. Chandrasekhar, C. Narsihmulu, S. S. Sultana, N. R. Reddy, *Org. Lett.* **2002**, *4*, 4399–440.

[36] D. Vinci, M. Donaldson, J. P. Hallett, E. A. John, P. Pollet, C. A. Thomas, J. D. Grilly, P. G. Jessop, C. L. Liotta, C. A. Eckert, *Chem. Commun*. **2007**, 1427–1429.

[37] X. Han, M. Poliakoff*, Chem. Soc. Rev*. **2012**, *41*, 1428–1436.

[38] a) R. D. Rogers, K. R. Seddon, *Science* **2003**, *302*, 792–793; b) J. Dupont, *Acc. Chem. Res.* **2011**, *44*, 1223–1231.

[39] C. Pretti, C. Chiappe, D. Pieraccini, M. Gregori, Fr. Abramo, G. Monni, L. Intorre, *Green Chem*. **2006**, *8*, 238–240.

[40] P. N. R. Vennestrøm, C. M. Osmundsen, C. H. Christensen, E. Taarning, *Angew. Chem. Int. Ed*. **2011**, *50*, 10502–10509.

[41] a) A. Corma, S. Iborra, A. Velty, *Chem. Rev.* **2007**, 107, 2411–2502; b) M. He, Y. Sun, B. Han, *Angew. Chem. Int. Ed.* **2013**, *52*, 9620–9633; c) P. Gallezot, *Chem. Soc. Rev.* **2012**, *41*, 1538–1558; d) G. W. Huber, A. Corma, *Angew. Chem. Int. Ed*. **2007**, *46*, 7184–7201.

[42] R. Sheldon, *Green Chem*. **2014**, *16*, 950–963.

[43] C. O. Tuck, E. Pérez, I. T. Horváth, R. A. Sheldon, M. Poliakoff, *Science* **2012**, *337,* 695–699.

[44] J. Zakzeski, P. C. A. Bruijnincx, A. L. Jongerius, B. M. Weckhuysen, *Chem. Rev.* **2010**, *110,* 3552–3599.

[45] U. Bornscheuer, K. Buchholz, J. Seibel, *Angew. Chem. Int. Ed*. **2014**, *53*, 10876–10893.

[46] a) P. Ferrini, R. Rinaldi, *Angew. Chem. Int. Ed*. **2014**, *53*, 8634–8639; b) A. Rahimi, A. Azarpira, H. Kim, J. Ralph, S. S. Stahl. *J. Am. Chem. Soc.* **2013**, *135*, 6415−6418; c) V. Molinari, C. Giordano, M. Antonietti, D. Esposito, *J. Am. Chem. Soc.* **2014**, *136*, 1758–1761.

[47] C. S. Lancefield, O. S. Ojo, F. Tran, N. J. Westwood, *Angew. Chem. Int. Ed*. **2015**, *54*, 258–262.

[48] Y. –B. Huang, Y. Fu, *Green Chem.* **2013**, *15*, 1095–1111.

[49] a) C. Chatterjee, F. Pong, A. Sen, *Green Chem.* **2015**, *17*, 40–71; b) M. J. Climent, A. Corma, S. Iborra, *Green Chem.* **2011**, *13*, 520–540; c) J. N. Chheda, G. W. Huber, J. A. Dumesic, *Angew. Chem. Int. Ed*. **2007**, *46*, 7164–7183; d) J. S. Luterbacher, D. Martin Alonsoa, J. A. Dumesic, *Green Chem*. **2014**, *16*, 4816–4838; e) H. Kobayashi, A. Fukuoka, *Green Chem*. **2013**, *15*, 1740–1763.

[50] A. J. J. Straathof, *Chem. Rev*. **2014**, *114*, 1871–1908.

[51] Y. S. Jang, J. Lee, A. Malaviya, D. Y. Seung, J. H. Cho, S. Y. Lee, *Biotechnol. J.* **2012**, *7*, 186–198.

[52] J. Rass-Hansen, H. Falsig, B. Jørgensen, C. H. Christensen, *J. Chem. Technol. Biotechnol*. **2007**, *82*, 329–333.

[53] a) B. N. van Leeuwen, A. M. van der Wulp, I. Duijnstee, A. J. van Maris, A. J. Straathof, *Appl. Microbiol. Biotechnol*. **2012**, *93*, 1377–1387; b) G. M. Whited, F. J. Feher, D. A. Benko, M. A. Cervin, G. K. Chotani, J. C. McAuliffe, R. J. LaDuca, E. A. Ben–Shoshan, K. J. Sanford, *Ind. Biotechnol*. **2010**, *6*, 152–163.

[54] K. N. G. Valdehuesa, H. Liu, G. M. Nisola, W.–J. Chung, S. H. Lee, S. J. Park, *Appl. Microbiol. Biotechnol*. **2013**, *97*, 309–332.

[55] a) G. Kaur, A. K. Srivasta, S. Chand, *Biochem. Eng. J*. **2012**, *64*, 106–118; b) R. K. Saxena, P. Anand, S. Saran, J. Isar, *Biotechnol. Adv.* **2009**, *27*, 895–913.

[56] S. Picataggio, T. Beardslee, *U.S. Pat* 8,241,879, 2012 to Verdezyne.

[57] M. Shiramizu, F. D. Toste, *Angew. Chem. Int. Ed*. **2012,** *51*, 8082–8086.

[58] A. M. Ruppert, K. Weinberg, R. Palkovits, *Angew. Chem. Int. Ed*. **2012**, *51*, 2564–2601.

[59] M. Rose, R. Palkovits, *ChemSusChem*, **2012**, *5*, 167−176.

[60] a) L. Hu, G. Zhao, W. Hao, X. Tang, Y. Sun, L. Lin, S. Liu, *RSC Adv.* **2012**, *2*, 11184–11206; b) V. Choudhary, S. H. Mushrif, C. Ho, A. Anderko, V. Nikolakis, N. S. Marinkovic, A. I. Frenkel, S. I. Sandler, D. G. Vlachos*, J. Am. Chem. Soc.* **2013**, *135*, 3997–4006; c) B. Li, S. Varanasib, P. Relue, *Green Chem*. **2013**, *15*, 2149–2157; d) P. Bhaumik, P. L. Dhepe, *ACS Catal*. **2013**, *3*, 2299−2303; e) V. Choudhary, S. I. Sandler, D. G. Vlachos, *ACS Catal*. **2012**, *2*, 2022−2028.

[61] a) A. A. Rosatella, S. P. Simeonov, R. F. M. Fradea, C. A. M. Afonso, *Green Chem*. **2011**, *13*, 754–793; b) D. Liua, E. Y.–X. Chen*, Green Chem*. **2014**, *16*, 964–981; c) R. –J. van Putten, J. C. van der Waal, E. de Jong, C. B. Rasrendra, H. J. Heeres, J. G. de Vries, *Chem. Rev*. **2013**, *113*, 1499−1597.

[62] a) J. B. Binder, R. T. Raines, *J. Am. Chem. Soc.* **2009**, *131*, 1979–1985; b) J. Donnelly, C. R. Müller, L. Wiermans, C. J. Chuck, P. D. de María, *Green Chem*. **2015**, *17*, 2714–2718; c) H. Wang, J. Male, Y. Wang, *ACS Catal*. **2013**, *3*, 1047−1070; d) D. Liu, E. Y. –X. Chen*, ACS Catal*. **2014**, *4*, 1302–1310.

[63] A. Gassama, C. Ernenwein, A. Youssef, M. Agach, E. Rigueta S. Marinković, B. Estrine, N. Hoffmann, *Green Chem*. **2013**, *15*, 1558–1566.

[64] a) P. –F. Koh, P. Wang, J. –M. Huang, T. –P. Loh, *Chem. Commun.* **2014**, *50*. 8324–8327; b) M. Mascal, S. Dutta, *Green Chem.* **2011**, *13*, 40–41.

[65] P. Tundo, M. Selva, *Acc. Chem. Res.* **2002**, *35,* 706–716.

[66] L. Lomba, B. Giner, I. Bandrés, C. Lafuente, M. R. Pino, *Green Chem*. **2011**, *13*, 2062–2070.

[67] N. S. Biradar, A. A. Hengne, S. N. Birajdar, R. Swami, C. V. Rode, *Org. Process Res. Dev*. **2014**, *18*, 1434–1442.

[68] M. G. Al-Shaal, A. Dzierbinski, R. Palkovits, *Green Chem*. **2014**, *16*, 1358–1364.

[69] F. Liguori, C. Moreno-Marrodan, P. Barbaro, *ACS Catal.* **2015**, *5*, 1882–1894.

[70] X. –L. Li, J. Deng, J. Shi, T. Pan, C. –G. Yu, H. –J. Xu, Y. Fu, *Green Chem*. **2015**, *17*, 1038–1046.

[71] M. O. Sonnati, S. Amigoni, E. P. T. de Givenchy, T. Darmanin, O. Choulet, F. Guittard, *Green Chem*. **2013**, *15*, 283–306.

[72] S. Lee, C. Shinji, K. Ogura, M. Shimizu, S. Maeda, M. Sato, M. Yoshida, Y. Hashimoto, H. Miyachi, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4895–4900.

[73] A. F. Watson, J. Liu, K. Bennaceur, C. J. Drummond, J. A. Endicott, B. T. Golding, R. J. Griffin, K. Haggerty, X. Lu, J. M. McDonnell, D. R. Newell, M. E. M. Noble, C. H. Revill, C. Riedinger, Q. Xu, Y. Zhao, J. Lunec, I. R. Hardcastle, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5916–5919.

[74] X. Huang, C. C. Cheng, T. O. Fischmann, J. S. Duca, M. Richards, P. K. Tadikonda, P. A. Reddy, L. Zhao, M. A. Siddiqui, D. Parry, N. Davis, W. Seghezzi, D. Wiswell, G. W. Shipps Jr., *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2590–2594.

[75] J. A. Spicer, G. Lena, D. M. Lyons, K. M. Huttunen, C. K. Miller, P. D. O'Connor, M. Bull, N. Helsby, S. M. F. Jamieson, W. A. Denny, A. Ciccone, K. A. Browne, J. A. Lopez, J. Rudd-Schmidt, I. Voskoboinik, J. A. Trapani, *J. Med. Chem*. **2013**, *56*, 9542−9555.

[76] a) A. Mertens, H. Zilch, B. Kdnig, W. Schuer, T. Poll, W. Kampe, H. Seidel, U. Leser, H. Leinert, *J. Med. Chem*. **1993**, *36*, 2526–2635; b) M. L. Curtin, R. R. Frey, H. R. Heyman, K. A. Sarris, D. H. Steinman, J. H. Holmes, P. F. Bousquet, G. A. Cunha, M. D. Moskey, A. A. Ahmed, L. J. Pease, K. B. Glaser, K. D. Stewart, S. K. Davidsen, Mi. R. Michaelides, *Bioorg. Med. Chem. Lett*. **2004**, *14*, 4505–4509; c) Z. –P. Zhuang, M. –P. Kung, M. Mu, H. F. Kung, *J. Med. Chem*. **1998**, *41*, 157–166; d) N. Kawanishi, T. Sugimoto, J. Shibata, K. Nakamura, K. Masutani, M. Ikuta, H. Hirai*, Bioorg. Med. Chem. Lett.* **2006**, *16*, 5122–5126; e) E. C. Lawson, D. K. Luci, S. Ghosh, W. A. Kinney, C. H. Reynolds, J. Qi, C. E. Smith, Y. Wang, L. K. Minor, B. J. Haertlein, T. J. Parry, B. P.

Damiano, B. E. Maryanoff*, J. Med. Chem*. **2009**, *52*, 7432–7445; f) S. Ito, Y. Hirata, Y. Nagatomi, A. Satoh, G. Suzuki, T. Kimura, A. Satow, S. Maehara, H. Hikichi, M. Hata, H. Ohta, H. Kawamoto, *Bioorg. Med. Chem. Lett*. **2009**, *19*, 5310–5313.

[77] S. –H. Zhang, C. –Y. Wang, Z. –Z. Jiang, P. –Z. Ni, J. –P. Zhou, B. –M. Xi, W. –H. Chen, *Chem. Pharm. Bull*. **2011**, *59*, 96–99.

[78] T. Lübbers, P. Angehrn, H. Gmünder, S. Herzig, *Bioorg. Med. Chem. Lett*. **2007**, *17*, 4708–4714.

[79] a) D. A. Favor, J. J. Powers, A. D. White, L. W. Fitzgerald, V. Groppi, K. A. Serpa, *Bioorg. Med. Chem. Lett*. **2010**, *20*, 5666–5669; b) T. R. Belliotti, W. A. Brink, S. R. Kesten, J. R. Rubin, D. J. Wustrow, K. T. Zoski, S. Z. Whetzel, A. E. Corbin, T. A. Pugsley, T. G. Heffner, L. D. Wise, *Bioorg. Med. Chem. Lett.***1998**, *8*, 1499–1502.

[80] M. Uno, H. S. Ban, H. Nakamura, *Bioorg. Med. Chem. Lett*. **2009**, *19*, 3166–3169.

[81] a) S. Sidique, R. –P. Dhanya, D. J. Sheffler, H. H. Nickols, L. Yang, R. Dahl, A. Mangravita-Novo, L. H. Smith, M. S. D'Souza, S. Semenova, P. J. Conn, A. Markou, N. D. P. Cosford, *J. Med. Chem*. **2012**, *55*, 9434−9445; b) R. –P. Dhanya, S. Sidique, D. J. Sheffler, H. H. Nickols, A. Herath, L. Yang, R. Dahl, R. Ardecky, S. Semenova, A. Markou, P. J. Conn, N. D. P. Cosford*, J. Med. Chem*. **2011**, *54*, 342–353.

[82] a) A. L. Ruchelman, H. –W. Man, W. Zhang, R. Chen, L. Capone, J. Kang, A. Parton, L. Corral, P. H. Schafer, D. Babusis, M. F. Moghaddam, Y. Tang, M. A. Shirley, G. W. Muller, *Bioorg. Med. Chem. Lett*. **2013**, *23,* 360–365; b) G. W. Muller, R. Chen, S. –Y. Huang, L. G. Corral, L. M. Wong, R. T. Patterson, Y. Chen, G. Kaplan, D. I. Stirling, *Bioorg. Med. Chem. Lett*. **1999**, *9,* 1625–1630.

[83] a) M. Lamblin, A. Couture, E. Deniau, P. Grandclaudon, *Tetrahedron* **2006**, *62*, 2917–2921; b) M. Lamblin, A. Couture, E. Deniau, P. Grandclaudon, *Org. Biomol. Chem*. **2007**, *5*, 1466–1471; c) T. Bousquet, J. –F. Fleury, A. Daïch, P. Netchitaïlo, *Tetrahedron* **2006**, *62*, 706–715; d) A. Moreau, M. Lorion, A. Couture, E. Deniau, P. Grandclaudon, *J. Org. Chem*. **2006**, *71*, 3303–3305; e) T. Shinozuka, Y. Yamamoto, T. Hasegawa, K. Saito, S. Naito, *Tetrahedron Lett*. **2008**, *49*, 1619–1622; f) M. Lamblin, A. Couture, E. Deniau, P. Grandclaudon, *Tetrahedron* **2007**, *63*, 2664–2669; g) S. Inoue, R. Kim, Y. Hoshinoa, K. Honda, *Chem. Commun*. **2006**, 1974–1976; h) K. H. Kim, H. J. Noh, S. U. Choi, K. R.

Lee, *J. Antibiot.* **2012**, *65*, 575–577; i) Y. Li, D. Liu, S. Cen, P. Proksch, W. Lin, *Tetrahedron* **2014**, *70*, 7010–7015; j) J. Yaegashi, M. B. Praseuth, S. –W. Tyan, J. F. Sanchez, R. Entwistle, Y. –M. Chiang, B. R. Oakley, C. C. C. Wang, *Org. Lett.* **2013**, *15*, 2862–2865.

[84] a) M. Angelin, P. Vongvilai, A. Fischer, O. Ramström, *Chem. Commun.* **2008**, *44*, 768–770; b) M. Angelin, M. Rahm, A. Fischer, T. Brinck, O. Ramström, *J. Org. Chem.* **2010**, *75*, 5882–5887; c) L. El Kaim, L. Grimaud, X F. Le Goff, A. Schiltz, *Org. Lett.* **2011**, *13*, 534–536; d) D. Augner, D. C. Gerbino, N. Slavov, J. –M. Neudörfl, H. –G. Schmalz, *Org. Lett.* **2011**, *13,* 5374–5377; e) A. A. Kilikli, C. Dengiz, S. Özcan, M. Balci, *Synthesis* **2011**, 3697–3705; f) M Ordóñez, G. D. Tibhe, A. Zamudio-Medina, J. L. Viveros-Ceballos, *Synthesis* **2012**, 569–574; g) P. Antico, V. Capaccio, A. Di Mola, A. Massa, L. Palombia, *Adv. Synth. Catal*. **2012**, *354*, 1717–1724; h) C. Petronzi, S. Collarile, G. Croce, R. Filosa, P. De Caprariis, A. Peduto, L. Palombi, V. Intintoli, A. Di Mola, A. Massa, *Eur. J. Org. Chem*. **2012**, 5357–5365; i) S. –C. Shen, X. –W. Sun, G. Q. Lin, *Green Chem.* **2013**, *15*, 896–900; j) K. Sakthivel, K. Srinivasan, *Eur. J. Org. Chem*. **2013**, 3386–3396; j) L. Zhang, J. B. Kim, D. O. Jang, *Tetrahedron Lett.* **2014**, *44*, 2654–2658; k) X. –W. Sun, M. Liu, M. –H. Xu, G. –Q. Lin, *Org. Lett.* **2008**, *10*, 1259–1262.

[85] a) L. Li, M. Wang, X. Zhang, Y. Jiang, D. Ma, *Org. Lett.* **2009**, *11*, 1309–1312; b) F. M. Irudayanathan, J. Noh, J. Choi, S. Lee, *Adv. Synth. Catal.* **2014**, *356*, 3433–3442; c) A. Gogoi, S. Guin, S. K. Rout, G. Majji B. K. Patel, *RSC Adv.* **2014**, *4*, 59902–59907.

[86] a) A. Salcedo, L. Neuville, J. Zhu*, J. Org. Chem*. **2008**, *73*, 3600–3603; b) G. Yang, W. Zhang, *Org. Lett*. **2012**, *14*, 268–271; c) G. Yang, C. Shen, W. Zhang, *Angew. Chem. Int. Ed.* **2012**, *51*, 9141–9145; d) N. Chatterjee, S. Sarkar, R. Pal, A. K. Sen, *Tetrahedron Lett.* **2013**, *54*, 3748–3751; e) J. Ju, C. Qi, L. Zheng, R. Hu, *Tetrahedron Lett.* **2013**, *54*, 5159–5161; f) W. Chen, L. Jin, Y. Zhu, X. Cao, L. Zheng, W. Mo, *Synlett* **2013**, *24*, 1856–1860; h) R. Mancuso, I. Ziccarelli, D. Armentano, N. Marino, S. V. Giofrè, B. Gabriele, *J. Org. Chem*. **2014**, *79*, 3506−3518; g) K. Natte, J. Chen, H. Li, H. Neumann, M. Beller, X. –F. Wu, *Chem. Eur. J*. **2014**, *20*, 14184–14188; h) H. H. Butani, D. D. Vachhani, U. C. Bhoya, A. K. Shah, E. V. Van der Eycken, *Eur. J. Org. Chem*. **2014**, 6634–6638; i) D. Wang, S. Cai, R. Ben, Y. Zhou, X. Li, J. Zhao, W. Wei, Y. Qian, *Synthesis* **2014**, *46*, 2045–2050; j) H. Cao, L. McNamee, H. Alper, *Org. Lett.* **2008**, *10*, 5281–5284; k) C. Sun, B. Xu, *J. Org. Chem*. **2008**, *73*, 7361–7364.

[87] a) W. C. Wertjes, L. C. Wolfe, P. J. Waller, D. Kalyani, *Org. Lett.* **2013**, *15*, 5986–5989; b) W. C. Wertjes, R. J. Waller, K. E. Shelton, D. Kalyani, *Synthesis* **2014**, *46*, 3033–3040.

[88] M. Fujioka, T. Morimoto, T. Tsumagari, H. Tanimoto, Y. Nishiyama, K. Kakiuchi, *J. Org. Chem*. **2012**, *77*, 2911−2923.

[89] B. S. Bhakuni, A. Yadav, S. Kumar, S. Patel, S. Sharma, S. Kumar, *J. Org. Chem*. **2014**, *79*, 2944−2954.

[90] L. Shi, L. Hu, J. Wang, X. Cao, H. Gu, *Org. Lett.* **2012**, *14*, 1876–1879.

[91] R. Sallio, S. Lebrun, N. Schifano-Faux, J. –F. Goossens, F. Agbossou-Niedercorn, E. Deniau, C. Michon, *Synlett* **2013**, *24*, 1785–1790.

[92] a) V. More, R. Rohlmann, O. G.Mancheño, C. Petronzi, L. Palombi, A. De Rosa, A. Di Molac, A. Massa *RSC Adv.* **2012**, *2*, 3592–3595; b) S. Tiso, L. Palombi, C. Vignes, A. Di Mola, A. Massa, *RSC Adv.* **2013**, *3*, 19380–19387.

[93] Y. Zhou, Y. Zhai, J. Li, D. Ye, H. Jiang H. Liu, *Green Chem.* **2010**, *12*, 1397–1404.

[94] V. Bisai, A. Suneja, V. K. Singh, *Angew. Chem. Int. Ed*. **2014**, *53*, 10737–10741.

[95] a) J. W. Wrigglesworth, B. Cox, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Org. Lett.* **2011**, *13*, 5326–5329; b) D. –D. Li, T. –T. Yuan G. –W. Wang, *Chem. Commun*. **2011**, *47*, 12789–12791; c) C. Zhu, J. R. Falck, *Org. Lett.* **2011**, *13*, 1214–1217.

[96] a) C. Zhu, J. R. Falck, *Chem. Commun*. **2012**, *48*, 1674–1676; b) K. D. Hesp, R. G. Bergman, J. A. Ellman, *Org. Lett.* **2012**, *14*, 2304–2307; c) C. Zhu, J. R. Falck, *Tetrahedron* **2012**, *68*, 9192–9199; d) B. Zhou, W. Hou, Y. Yang, Y. Li, *Chem. Eur. J*. **2013**, *19*, 4701–4706.

[97] D. M. Shacklady-McAtee, S. Dasgupta, M. P. Watson, *Org. Lett.* **2011**, *13*, 3490–3493.

[98] X. G. Li, M. Sun, K. Liu, P. N. Liu, *Adv. Synth. Catal.* **2015**, *357*, 395–399.

[99] R. Manoharan, M. Jeganmohan, *Chem. Commun.* **2015**, *51*, 2929–2932.

[100] K. Smith, G. A. El-Hiti, A. S. Hegazy, *Chem. Commun*. **2010**, *46*, 2790–2792.

[101] S. Adachi, M. Onozuka, Y. Yoshida, M. Ide, Y. Saikawa, M. Nakata, *Org. Lett*. **2014**, *16*, 358−361.

[102] a) R. J. Huntley, M. Gurram, J. R. Walker, D. M. Jenkins, E. J. Robé, F. Ahmed, *Tetrahedron Lett.* **2014**, *55*, 2286–2289; b) B. Liu, E. Wei, S. Lin, B. Zhao, F. Liang, *Chem. Commun*. **2014**, *50*, 6995–6997; c) E. Gopi I. N. N. Namboothiri, *J. Org. Chem.* **2014**, *79*, 7468−7476; d) X. Huang, J. Xu, *J. Org. Chem.* **2009**, *74*, 8859–8861.

[103] F. Ling, Z. Li, C. Zheng, X. Liu, C. Ma, *J. Am. Chem. Soc*. **2014**, *136,* 10914−10917.

[104] W. Reppe, O. Schichting, K. Klager, T. Toepel, *Justus Liebigs Ann. Chem.* **1948**, *560*, 1–92.

[105] For recent reviews of [2+2+2]-cyclotrimerizations refer to a) S. Saito, Y. Yamamoto, *Chem. Soc. Rev.* **2000**, *100*, 2901−2915; b) J. Varela, C. Saá, *Chem. Rev.* **2003**, *103*, 3787−3801; c) S. Kotha, E. Brahmachary, K. Lahiri, *Eur. J. Org. Chem.* **2005**, 4741–4767; d) P. Chopadea, J. Louie, *Adv. Synth. Catal.* **2006**, *348*, 2307–2327; e) V. Gandon, C. Aubert, M. Malacria, *Chem. Commun.* **2006**, 2209–2217; e) B. Galan, T. Rovis, *Angew. Chem. Int. Ed.* **2009**, *48*, 2830–2834; f) G. Domínguez, Javier Pérez-Castells, *Chem. Soc. Rev.* **2011**, *40*, 3430–3444; g) M. R. Shaaban, R. El-Sayed, A. H. M. Elwahya, *Tetrahedron* **2011**, *67*, 6095–6130; h) Y. Shibata, K. Tanaka, *Synthesis* **2012**, *44*, 323–350.

[106] S. Saito, Y. Yamamoto, *Chem. Rev.* **2000**, *100*, 2901−2915.

[107] Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933.

[108] V. Gevorgyan, U. Radhakrishnan, A. Takeda, M. Rubina, M. Rubin, Y. Yamamoto, *J. Org. Chem.* **2001**, *66*, 2835–2841.

[109] For recent examples refer to: a) R. Takeuchi, Y. Nakaya, *Org. Lett.* **2003**, *5*, 3659–3662; b) R. Tanaka, A. Yuza, Y. Watai, D. Suzuki, Y. Takayama, F. Sato, H. Urabe, *J. Am. Chem. Soc.* **2005**, *127*, 7774–7780; c) G. Onodera, M. Matsuzawa, T. Aizawa, T. Kitahara, Y. Shimizu, S. Kezuka, R. Takeuchi, *Synlett* **2008**, 755–758; d) C. Wang, X. Li, F. Wu, B. Wan, *Angew. Chem. Int. Ed.* **2011**, *50*, 7162–7166.

[110] a) K. P. C. Vollhardt, R. G. Bergman, *J. Am. Chem. Soc.* **1974**, *96*, 4996–4998; b) W. C. L. Aalbersberg, A. J. Barkovich, R. L. Funk, R. L. Hillard III, K. P. C. Vollhard, *J.*

Am. Chem. Soc. **1975**, *97*, 5600–5602; c) R. L. Hillard III, K. P. C. Vollhurt, *Angew. Chem. Int. Ed.* **1975**, *14*, 712–713; d) R. L. Hillard III, K. P. C. Vollhurt, *J. Am. Chem. Soc.* **1977**, *99*, 4058–4069.

[111] S. Kezuka, S. Tanaka, T. Ohe, Y. Nakaya, R. Takeuchi, *J. Org. Chem.* **2006**, *71*, 543–552.

[112] S. H. Lecker, N. H. Nguyen, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1986**, *108*, 856–858.

[113] a) M. Petit, G. Chouraqui, P. Phansavath, C. Aubert, M. Malacria, *Org. Lett.* **2002**, *4*, 1027–1029; b) G. Chouraqui, M. Petit, C. Aubert, M. Malacria, *Org. Lett.* **2004**, 1519–1521; c) G. Chouraqui, M. Petit, P. Phansavath, C. Aubert, M. Malacria, *Eur. J. Org. Chem.* **2006**, 1413–1421.

[114] A. H. M. Elwahy, K. Hafner, *Tetrahedron Lett.* **2001**, *51*, 1313–1316.

[115] a) A. Maderna, H. Pritzkow, W. Siebert, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1501–1503; b) C. Ester, A. Maderna, H. Pritzkow, W. Siebert, *Eur. J. Inorg. Chem.* **2000**, 1177–1184.

[116] N. Saino, F. Amemiya, E. Tanabe, K. Kase, S. Okamoto, *Org. Lett.* **2006**, *8*, 1439–1442.

[117] A. Goswami, T. Ito, S. Okamoto, *Adv. Synth. Catal.* **2007**, *349*, 2368–2374.

[118] Y. Sugiyama, R. Kato, T. Sakurada, S. Okamoto, *J. Am. Chem. Soc.* **2011**, *133*, 9712–9715.

[119] N. Saino, T. Kawaji, T. Ito, Y. Matsushita, S. Okamoto, *Tetrahedron Lett.* **2010**, *51*, 1313–1316.

[120] E. Müller, *Synthesis* **1974**, 761–774.

[121] R. Grigg, R. Scott, P. Stevenson, *Tetrahedron Lett*. **1982**, *23*, 2691–2692.

[122] D. D. Young, R. S. Senaiar, A. Deiters, *Chem. Eur. J.* **2006**, *12*, 5563–5568.

[123] a) Y. –T. Wu, A. Linden, J. S. Siegel, *Org. Lett.* **2005**, *7*, 4353–4355; b) Y. –T. Wu, T. Hayama, K. K. Baldridge, A. Linden, J. S. Siegel, *J. Am. Chem. Soc.* **2006**, *128*, 6870–6884.

[124] C. V. Ramana, S. R. Salian, R. G. Gonnad, *Eur. J. Org. Chem.* **2007**, 5483–5486.

[125] Y. Komine, A. Kamisawa, K. Tanaka, *Org. Lett.* **2009**, *11*, 2361–2364.

[126] a) K. Tanaka, G. Nishida, M. Ogino, M. Hirano, K. Noguchi, *Org. Lett.* **2005**, *7*, 3119–3121; b) G. Nishida, K. Noguchi, M. Hirano, K. Tanaka, *Angew. Chem. Int. Ed.* **2007**, *46*, 3951–3954.

[127] G. Nishida, K. Noguchi, M. Hirano, K. Tanaka, *Angew. Chem.* **2008**, *120*, 3458–3461.

[128] T. Suda, K. Noguchi, M. Hirano, K. Tanaka, *Chem. Eur. J.* **2008**, *14*, 6593–6596.

[129] a) K. Tanaka, H. Sagae, K. Toyoda, K. Noguchi, *Eur. J. Org. Chem.* **2006**, 3575–3581; b) L. Iannazzo, K. P. C. Vollhardt, M. Malacria, C. Aubert, V. Gandon, *Eur. J. Org. Chem.* **2011**, 3283–3292.

[130] S. Kezuka, S. Tanaka, T. Ohe, Y. Nakaya, R. Takeuchi, *J. Org. Chem.* **2006**, *71*, 543–552.

[131] R. Takeuchi, S. Kezuka, *Synthesis* **2006**, *20*, 3349–3366.

[132] T. Matsuda, S. Kadowaki, T. Goya, M. Murakami, *Org. Lett*. **2007**, *9*, 133–136.

[133] T. Shibata, T. Fujimoto, K. Yokota, K. Takagi, *J. Am. Chem. Soc.* **2004**, *126*, 8382–8383.

[134] a) J. –U. Peters, S. Blechert, *Chem. Commun.* **1997**, 1983–1984; b) S. K. Das, R. Roy, *Tetrahedron Lett.* **1999**, *40*, 4015–4018; c) B. Witulski, T. Stengel, J. M. Fernández-Hernández, *Chem. Commun.* **2000**, 1965–1966; d) G. B. Hoven, J. Efskind, C. Romming, K. Undheim, *J. Org. Chem.* **2002**, *67*, 2459–2463.

[135] Á. Mallagaray, S. Medina, G. Domínguez, J. Pérez-Castells, *Synlett* **2010**, 2114–2118.

[136] a) Y. Yamamoto, R. Ogawa, K. Itoh, *Chem. Commun.* **2000**, 549–550; b) Y. Yamamoto, K. Hata, T. Arakawa, K. Itoh, *Chem. Commun.* **2003**, 1290–1291; c) Y. Yamamoto, T. Arakawa, R. Ogawa, K Itoh, *J. Am. Chem. Soc.* **2003**, *125*, 12143–12160;

d) Y. Yamamoto, T. Saigoku, T. Ohgai, H. Nishiyamaa, K. Itoh, *Chem. Commun.* **2004**, 2702–2703; e) Y. Yamamoto, J. –I Ishii, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2004**, *126*, 3712–3713; f) Y. Yamamoto, K. Kinpara, T.Sagoku, H. Takagashi, S. Okuda, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2005**, *127*, 605–613; h) Y. Yamamoto, J. –I. Ishii, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2005**, *127*, 9625–9631; g) Y. Yamamoto, K. Hattori, J. –I. Ishii, H. Nishiyama, K. Itoh, *Chem. Commun.* **2005**, 4438–4440; h) Y. Yamamoto, T. Saigoku, H. Nishiyama, T. Ohgai, K. Itoh, *Org. Biomol. Chem.* **2005**, *3*, 1768–1775; i) Y. Yamamoto, T. Hashimoto, K. Hattori, M. Kikuchi, H. Nishiyama, *Org. Lett.* **2006**, *8*, 3565–3568.

[137] Y. Yamamoto, K. Kinpara, T. Saigoku, H. Nishiyama, K. Itoh, *Org. Biomol. Chem*. **2004**, *2*, 1287–1294.

[138] K. Kirchner, M. J. Calhorda, R. Schmid, L. F. Veiros, *J. Am. Chem. Soc.* **2003**, *125*, 11721–11729.

[139] I. Fleming, S. Gill, A. K. Sarkar, T. Schmidlin, *J. Chem. Soc. Perkin Trans. 1* **1992**, 3351–3361.

[140] W. Hess, J. W. Burton, *Chem. Eur. J.* **2010**, *16*, 12303–12306.

[141] a) B. Witulski, T. Stengel, *Angew. Chem. Int. Ed.* **1999**, *38*, 2426–2430; b) B. Witulski, A. Zimmermann, *Synlett* **2002**, 1855–1859; c) B. Witulski, C. Alayrac, *Angew. Chem. Int. Ed.* **2002**, *41*, 3281–3284.

[142] C. Ester, A. Maderna, H. Pritzkow, W. Siebert, *Eur. J. Inorg. Chem*. **2000**, 1177–1184.

[143] B. Witulski, T. Stengel, J. M. Fernández-Hernández, *Chem. Commun*. **2000**, 1965–1966.

[144] Q. Li, A. V. Rukavishnikov, P. A. Petukhov, T. O. Zaikova, C. Jin, J. F. W. Keana, *J. Org. Chem.* **2003**, *68*, 4862–4869.

[145] G. A. Molander, F. Cadoret, *Tetrahedron Lett.* **2011**, *52*, 2199–2202.

[146] C. Blanchard, E. Framery, M. Vaultier, *Synthesis* **1996**, 45–47.

[147] A. Nudelman, Y. Binnes, N. Shmueli-Broidea, Y. Odessa, J. P. Hieble, A. C. Sulpizio, *Arch. Pharm. Pliarm. Med. Chem.* **1996**¸ *329,* 125–132.

[148] Y. Li, T. J. Marks, *J. Am. Chem. Soc.* **1998**, *120*, 1757–1771.

[149] J. Clayden, L. Vallverdu, J. Clayton, M. Helliwell, *Chem. Commun.* **2008**, 561–563.

[150] S. L. MacNeil, M. Gray, D. G. Gusev, L. E. Briggs, V. Snieckus, *J. Org. Chem.* **2008**, *73*, 9710–9719.

[151] G. Lopez-Valdez, S. Oliguín-Uribe, L. D. Miranda, *Tetrahedron Lett.* **2007**, *48*, 8285–8289.

[152] T. Abe, H. Takeda, Y. Takahashi, Y. Miwa, K. Yamada, M. Ishikura, *Eur. J. Org. Chem*. **2010**, 3281–3294.

[153] Z. Zhao, V. Snieckus, *Org. Lett.* **2005**, *7*, 2523–2526.

[154] M. D. Clift, R. B. Silverman, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3122–3125.

[155] Pfizer Limited; Pfizer Inc., **2004**, Therapeutic Use of Aryl Amino Acid Derivatives, US Patent WO2004/14357 A2.

[156] W. B. Motherwell, G Bégis, D. E. Cladingboel, L. Jerome, T. D. Sheppard, *Tetrahedron* **2007**, *63*, 6462–6476.

[157] A. Arizpe, F. J. Sayago, A. I. Jiménez, M. Ordóñez, C. Cativiela, *Eur. J. Org. Chem.* **2011**, 6732–6738.

[158] K. Maruyoshi, K. Nonaka, T. Sagane, T. Demura, T. Yamaguchi, N. Matsumori, T. Oishi, M. Murata, *Chem. Eur. J.* **2009**, *15*, 1618–1626.

[159] H. Chiba, S. Oishi, N. Fujii, H. Ohno, *Angew. Chem. Int. Ed.* **2012**, *51*, 9169–9172.

[160] G. –S. J. Wang, *Ethnopharmacology* **1989**, *26*, 147–162.

[161] D. J. Karras, S. E. Farrell, R. A. Harrigan, F. M. Henretig, L. Gealt, *Am. J. Emerg. Med*. **1996**, *14*, 478–483.

[162] A. McCluskey, M. C. Bowyer, E. Collins, A. T. R. Sim, J. A. Sako, M. L. Baldwin, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1687–1690.

[163] A. McCluskey, S. P. Ackland, M. C. Bowyer, M. L. Baldwin, J. Garner, C. C. Walkom, J. A. Sakoff, *Bioorg. Chem.* **2003**, *31*, 66–77.

[164] D. Tagwireyi, D. E. Ball, P. J. Loga, S. Moyo, *Toxicon*. **2000**, *38*, 1865.

[165] a) J. Bajsa, A. McCluskey, C. P. Gordon, S. G. Stewart, T. A. Hill, R. Sahu, S. O. Duke, B. L. Tekwani, *Bioorg. Med. Chem. Lett.* **2010**, *20,* 6688–6695; b) G. –C. Wang, J. Xiao, L. Yu, J. –S. Li, J. –R. Cui, R. Q. Wang, F. –X. Ran*, J. Organomet. Chem*. **2004**, *689*, 1631–1638; c) L. –P. Deng, F. –M. Liu, H. –Y. Wang, *J. Heterocyclic Chem.* **2005**, *42*, 13–18; d) Y. Zhou, T. Jiang, S. Ren, J. Yu, Z. Xia, *J. Organomet. Chem.* **2005**, *690*, 2186–2190.

[166] H. L. Kok, C. H. Chui, W. S. Lam, J. Chen, F. Y. Lau, R. S. M. Wong, G. Y. M. Cheng, P. B. S. Lai, T. W. T. Leung, M. W. Y. Yu, J. C. O. Tang, A. S. C. Chan, *Bioorg. Med. Chem. Lett.* **2007**, *17,* 1155–1159.

[167] R. M. Attar, M. Jure-Kunkel, A. Balog, M. E. Cvijic, J. Dell-John, C. A. Rizzo, L. Schweizer, T. E. Spires, J. S. Platero, M. Obermeier, W. Shan, M. E. Salvati, W. R. Foster, J. Dinchuk, S. –J. Chen, G. Vite, R. Kramer, M. M. Gottardis, *Cancer Res.* **2009**, *69*, 6522–6530.

[168] M. J. Robertson, C. P. Gordon, J. Gilbert, A. McCluskey, J. A. Sakoff, *Bioorg. Med. Chem*. **2011**, *19,* 5734–5741.

[169] a) M. Lanier, D. Schade, E. Willems, M. Tsuda, S. Spiering, J. Kalisiak, M. Mercola, J. R. Cashman, *J. Med. Chem*. **2012**, *55*, 697−708; b) J. Bajsa, A. McCluskey, C. P. Gordon, S. G. Stewart, T. A. Hill, R. Sahu, S. O. Duke, B. L. Tekwani *Bioorg*. *Med. Chem. Lett*. **2010**, *20*, 6688–6695.

[170] C. K. Jones, D. W. Engers, A. D. Thompson, J. R. Field, A. L. Blobaum, S. R. Lindsley, Y. Zhou, R. D. Gogliotti, S. Jadhav, R. Zamorano, J. Bogenpohl, Y. Smith, R. Morrison, J. S. Daniels, C. D. Weaver, P. J. Conn, C. W. Lindsley, C. M. Niswender, C. R. Hopkins, *J. Med. Chem*. **2011**, *54*, 7639−7647.

[171] J. Zhang, G. A. Lawrance, N. Chau, P. J. Robinson, A. McCluskey, *New J. Chem.* **2008***, 32,* 28–36.

[172] B. E. Campbell, M. Tarleton, C. P. Gordon, J. A. Sakoff, J. Gilbert, A. McCluskey, R. B. Gasser, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3277–3281.

[173] a) R. N. Misra, B. R. Brown, P. M. Sher, M. M. Patel, S. E. Hall, W. –C. Han, J. C. Barrish, O. Kocy, D. N. Harris, H. J. Goldenberg, I. M. Michel, W. A. Schumacher, M. L. Webb, H. Monshizadegan, M. L. Ogletree*, J. Med. Chem*. **1993**, *36*, 1401–1417; b) M. L. Ogletree, D. N. Harris, R. Greenberg, M. F. Haslanger, M. Nakane, *J. Pharm. Exp. Ther.* **1985**, *2*, 435–441; c) M. Sodeoka, Y. Baba, S. Kobayashi, N. Hirukawa, *Bioorg. Med. Chem. Lett*. **1997**, *7*, 1833–1836; d) M. E. Hart, A. R. Chamberlin, C. Walkom, J. A. Sakoff, A. McCluskey, *Bioorg. Med. Chem. Lett*. **2004**, *14*, 1969–1973; e) A. Enz, G. Zenke, E. Pombo-Villar, *Bioorg. Med. Chem. Lett*. **1997**, *7*, 2513–2518.

[174] S. G. Stewart, T. A. Hill, J. Gilbert, S. P. Ackland, J. A. Sakoff, A. McCluskey, *Bioorg. Med. Chem.* **2007**, *15*, 7301–7310.

[175] H. –B. Zhou, J. S. Comninos, F. Stossi, B. S. Katzenellenbogen, J. A. Katzenellenbogen, *J. Med. Chem.* **2005**, *48*, 7261–7274.

[176] R. Dhanapal, P. T. Perumal, C. Ramprasathc, N. Mathivanan, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3599–3603.

[177] a) P. Vogel, D. Fattori, F. Gasparini, C. Le Drian, *Synlett* **1990**, *4*, 173–185; b) T. Hudlicky, D. A. Entwistle, K. K. Pitzer, A. J. Thorpe, *Chem. Rev.* **1996**, *96*, 1195−1220; c) P. A. Grieco, R. E. Zelle, R. Lis, J. Finn, *J. Am. Chem. Soc.* **1983**, *105*, 1403–1404; d) J. Y. Sim, G. –S. Hwang, K. H. Kim, E. M. Ko, D. H. Ryu, *Chem. Commun.* **2007**, 5064–5065; e) M. Shoji, Y. Hayashi, *Eur. J. Org. Chem.* **2007**, 3783–3800; f) M. Shoji, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1672–1690.

[178] a) M. Tori, T. Torii, K. Tachibana, S. Yamada, T. Tsuyuki, T. Takahashi, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 469–472; b) Y. Yamano, M. Ito, A. Wada, *Org. Biomol. Chem.* **2008**, *6*, 3421–3427; c) C. –L. Lee, L. –C. Chiang, L. –H. Cheng, C. –C. Liaw, M. H. A. El-Razek, F. –R. Chang, Y. –C. Wu, *J. Nat. Prod.* **2009**, *72*, 1568–1572; d) A. Kusano, M. Shibano, G. Kussano, T. Miyase, *Chem. Pharm. Bull.* **1996**, *44*, 2078–2085; e) E. N. Pitsinos, N. Athinaios, V. P. Vidali, *Org. Lett.* **2012**, *14*, 4666–4669; f) A. Yajima, F. Saitou, M. Sekimoto, S. Maetoko, T. Nukada, G. Yabuta, *Tetrahedron* **2005**, *61*, 9164–9172; g) Y. –T. Lin, F. –Y. Lin, M. Isobe, *Org. Lett.* **2014**, *16*, 5948–5951.

[179] O. Diels, K. Alder, *Ber. Dtsch. Chem. Ges*. **1929**, *62*, 554–562.

[180] a) R. B. Woodward, H. Baer, *J. Am. Chem. Soc.* **1948**, *70*, 1161–1166; b) M. W. Lee, W. C. Hemdon*, J. Org. Chem.* **1978**, *43*, 518–518; c) M. J. S. Dewar, A. B. Pierini, *J. Am. Chem. Soc*. **1984**, *106*, 203–208.

[181] Y. Tachibana, M. Yamahata K. Kasuya, *Green Chem*. **2013**, *15*, 1318–1325.

[182] L. Rulíšek, P. Šebek, Z. Havlas, R. Hrabal, P. Čapek, A. Svatoš, *J. Org. Chem.* **2005**, *70*, 6295–6302.

[183] R. C. Boutelle, B. H. Northrop*, J. Org. Chem*. **2011**, *76*, 7994–8002.

[184] G. H. Grogan, L. M. Rice, *J. Med. Chem.* **1963**, *6*, 802–805.

[185] H. Kwart, I. Burchuk, *J. Am. Chem. Soc.* **1951**, *74*, 3094–3097.

[186] a) S. Jarosz, M. Mach, K. Szewczyk, S. Skóra, Z. Ciunik, *Eur. J. Org. Chem.* **2001**, 2955–2964; b) S. J. Howell, N. Spencer, D. Philp, *Org. Lett.* **2002***, 4*, 273–276.

[187] a) H. Kotsuki H. Nishizawa, *Heterocycles* **1981**, *16*, 1287–1291; b) H. Kotsuki, H. Nishizawa, M. Ochi, K. Matsuoka, *Bull. Chem. Soc. Jap.* **1982**, *55*, 496–499; c) A. McCluskey, M. A. Keane, C. C. Walkom, M. C. Bowyer, A. T. R. Sim, D. J. Young, J. A. Sakoff, *Bioorg. Med. Chem. Lett.* **2012**, *12*, 391–393.

[188] a) $BF_3.OEt_2$: H. Kotsuki, K. Asao, H. Ohnishi, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3339–3340; b) $Cu(BF_4)_2$: J. A. Moore, E. M. Partain, *J. Org. Chem*. **1983**, *48*, 1105–1106; c) ZnI_2: F. Brion, *Tetrahedron Lett*. **1982**, *23*, 5299–5302; d) Oxazaborolidinone: Ram S. Singh, S. Adachi, F. Tanaka, T. Yamauchi, C. Inui, T. Harada, *J. Org. Chem*. **2008**, *73*, 212–218; e) Et_2AlCl: S. D. Townsend, X. Wu, S. J. Danishefsky, *J. Am. Chem. Soc*. **2012**, *134*, 10659–10663; f) BCl_3: B. Garrigues, A. Oussaid, *J. Organomet. Chem*. **1999**, *585*, 253–255; g) $LiClO_4$: P. A. Grieco, J. J. Nunes, M. D. Gaul, *J. Am. Chem. Soc*. **1990**, *112*, 4595–4596; h) $MgSiO_3$: V. V. Veselovsky, A. S. Gybin. A. V. Lozanova, A. M. Molseenkov, W. A. Smit, R. Cable, *Tetrahedron Lett*. **1888**, *29*, 175–178.

[189] Y. Hayashi, M. Nakamura, S. Nakao, T. Inoue, M. Shoji, *Angew. Chem. Int. Ed.* **2002**, *41*, 4079–4082.

[190] M. N. Pennell, R. W. Foster, P. G. Turner, H. C. Hailes, C. J. Tame, T. D. Sheppard, *Chem. Commun.* **2014**, *50*, 1302–1304.

[191]a) A Murai, K. Takahashi, H. Taketsuru, T. Masamune, *J. Chem. Soc., Chem. Commun.* **1981**, 221–222; b) G. E. Daia, C. D. Gabbutt, J. D. Hepworth, B. M. Heron, D. E. Hibbs, M. B. Hursthouse, *Tetrahedron Lett.* **2002**, *43*, 4507–4510; c) A. B. Smith, N. J. Liverton, N. J. Hrib, H. Sivaramakrishnan, K. Winzenberg, *J. Am. Chem. Soc.* **1986**, *108*, 3040–3048.

[192] Z. Fei, W. Kong, H. Wang, J. Peng, F. Sun, Y. Yin, J. Bajwa, X. Jiang, *Org. Process Res. Dev.* **2012**, *16*, 1436–1441.

[193] S. P. Borikar, V. Paul, V. G. Puranik, V. T Sathe, S. Lagunas-Rivera, M. Ordónez, *Synthesis* **2011**, 1595–1598.

[194] Dihedral angles were calculated using ChemBio3D Ultra® following an MM2 structure optimization.

[195] N. Garg, M. Larhed, A. Hallberg, *J. Org. Chem.* **1998**, *63*, 4158–4162.

[196] W. Schepens, D. Van Haver, M. Vandewalle, R. Bouillon, A. Verstuyf, P. J. De Clercq, *Org. Lett*. **2006**, *8*, 4247–4250.

[197] H. van de Waterbeemd, E. Gifford, *Nat. Rev. Drug Discovery* **2003**, *2*, 192–204.

[198] a) P. D. Leeson, B. Springthorpe, *Nat. Rev. Drug Discovery* **2007**, *6*, 881–890; b) P. Gleeson, G. Bravi, S. Modi, D. Lowe, *Bioorg*. *Med. Chem.* **2009**, *17*, 5906–5919; c) J. D. Hughes, J. Blagg, D. A. Price, S. Bailey, G. A. DeCrescenzo, R. V. Devraj, E. Ellsworth, Y. M. Fobian, M. E. Gibbs, R. W. Gilles, N. Greene, E. Huang, T. Krieger-Burke, J. Loesel, T. Wager, L. Whiteley, Y. Zhang, *Bioorg. Med. Chem. Lett*. **2008**, *18*, 4872–4875.

[199] C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Delivery Rev*. **1997**, *23*, 3–25.

[200] J. Linnankoski, J. M Mäkelä, V. –P. Ranta, A. Urtti, M. Yliperttula, *J. Med. Chem.* **2006**, *49*, 3674–3681.

[201] S. J. Teague, A. M. Davis, P. D. Leeson, T. Oprea, *Angew. Chem. Int. Ed.* **1999**, *38*, 3743–3748.

[202] A. Nadin, C. Hattotuwagama, I. Churcher, *Angew. Chem. Int. Ed*. **2012**, *51*, 1114–1122.

[203] P A. Clemons, N. E. Bodycombe, H. A. Carrinski, J. A. Wilson, A. F. Shamji, B. K. Wagner, A. N. Koehler, S. L. Schreiber, *Proc. Natl. Acad. Sci. USA* **2011**, *107*, 18787–18792.

[204] M. C. Sanguinetti, M. Tristani-Firouzi, *Nature* **2006**, *440*, 463–469.

[205] D. Tobia, R. Harrison, B. Phillips, T. L. White, M. DiMare, B. Rickborn, *J. Org. Chem.* **1993**, *58*, 6701–6706.

[206] **Gaussian09 Reference**: Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009

[207] a) S. Danishefsky, T. Kitahara, *J. Am. Chem. Soc*. **1974**, *96*, 7807–7808; b) S. A. Kozmin, V. H. Rawal, *J. Org. Chem.* **1997**, *62*, 5252–5253; c) J. M. Holmes, A. L. Albert, M. Gravel*, J. Org. Chem*. **2009**, *74*, 6406–6409; d) S. Zhou, E. Sánchez–Larios, M. Gravel*, J. Org. Chem*. **2012**, *77*, 3576–3582; e) J. Choi, H. Park, H. J. Yoo, S. Kim, E. J. Sorensen, C. Lee, *J. Am. Chem. Soc.* **2014**, *136*, 9918–9921.

[208] a) M. Gütschow, T. Hecker, A. Thiele, S. Hauschild, K. Eger, *Bioorg. Med. Chem.* **2001**, *9*, 1059–1065; b) E. J. C. de-Blanco, B. Pandit, Z. Hu, J. Shi, A. Lewis P. –K. Li, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6031–6035; c) L. M. Lima, P. Castro, A. L. Machado, C. A. M. Fraga, C. Lugnier, V. L. G. de Moraes, E. J. Barreiro, *Bioorg. Med. Chem.* **2002**, *10*, 3067–3073.

[209] J. B. Aragon-Ching, H. Li, E. R. Gardner, W. D. Figg, *Recent Pat. Anticancer Drug Discov*. **2007**, *2*, 167–174.

[210] a) P. Uebelhart, C. Weymuth, H. –J. Hansen, *Helv. Chim. Acta* **2005**, *88*, 1250–1290; b) K. –S. Yeung, N. A. Meanwell, Y. Li, Q. Gao, *Tetrahedron Lett*. **1998**, *39*, 1483–1486; c) A. Pelter, B. Singaram, *Tetrahedron Lett.* **1982**, *23*, 245–258.

[211] E.Z. Oblak, M. D. VanHeyst, J. Li, A. J. Wiemer, D. L. Wright, *J. Am. Chem. Soc.* **2014**, *136*, 4309−4315.

[212] a) G. Romeo, U. Chiacchio, A. Corsaro, P. Merino, *Chem. Rev*. **2010**, *110*, 3337–3370; b) L. P. Jordheim, D. Durantel, F. Zoulim, C. Dumontet, *Nature Rev. Drug Discov.* **2012**, *12*, 447–464.

[213] W. –S. Wang, C. –H. Tzeng, T. –J. Chiou, J. –H. Liu, R. –K. Hsieh, C. –C. Yen, P. –M. Chen, *Jpn. J. Clin. Oncol.* **1997**, *27,* 154–157.

[214] E. De Clercq, *J. Med. Chem.* **1986**, *29*, 1561–1569.

[215] R. Yarchoan, H. Mitsuya, C. Myers, S. Broder, *N. Engl. J. Med.* **1989**, *321*, 726–738.

[216] A. Leonardi, J. P. Hieble, L. Guarneri, D. P. Naselsky, E. Poggesi, G. Sironi, A. C. Sulpizio, R. Testa, *J. Pharm. Exp. Ther*. **1997**, *281*, 1272–1283.

[217] D. J. Martin, P. Lluel, E. Guillot, A. Coste, D. Jammes, I. Angel, *J. Pharm. Exp. Ther*. **1997**, *282,* 228–235.

[218] J. Eron, Jr., P. Yeni, J. Gathe, Jr., V. Estrada, E. DeJesus, S. Staszewski, P. Lackey, C. Katlama, B. Young, L. Yau, D. Sutherland-Phillips, P. Wannamaker, C. Vavro, L. Patel, J. Yeo, M. Shaefer, *Lancet* **2006**, *368*, 476–482.

[219] J. Hao, B. Chen, Y. Yao, M. Hossain, T. Nagatomo, H. Yao, L. Kong, H. Sun, *Bioorg. Med. Chem. Lett*. **2012**, *22,* 3441–3444.

[220] W. H. R. Auld, W. R. Murdoch, *BMJ*, **1971**, *4*, 786–788.

[221] a)X. Qiu, G. –D. Zhao, L. –Q. Tang, Z. –P. Liu, *Bioorg. Med. Chem. Lett*. **2014**, *24*, 2465–2468; b) S. Thaisrivongs, J. W. Strohbach, *Biopolymers* **1999**, *51*, 51–59; c) C. G. Carolan, G. P. Dillon, D. Khan, S. A. Ryder, J. M. Gaynor, S. Reidy, J. F. Marquez, M. Jones, V. Holland, J. F. Gilmer, *J. Med. Chem*. **2010**, *53*, 1190–1199.

[222] a) H. Kobayashi, H. Yokoyama, B. Feng, A. Fukuoka, *Green Chem.* **2015**, *17*, 2732–2735; b) R. Palkovits, K. Tajvidi, J. Procelewska, R. Rinaldi, A. Ruppert, *Green Chem***. 2010**, *12*, 972–978.

[223] K. M. Tomczyk, P. A. Guńka, P. G. Parzuchowski, J. Zachara, G. Rokicki, *Green Chem*. **2012**, *14*, 1749–1758.

[224] a) P. Crotti, V. Di Bussolo, L. Favero, C. Gozzi, M. Pineschi, *Tetrahedron: Asymmetry* **1997**, *8*, 1611–1621; b) L. M. H. Leung, V. Gibson, B. Linclau, *Tetrahedron: Asymmetry* **2005**, *16*, 2449–2453; c) J. S. Edmonds, Y. Shibata, F. Yang, M. Morita, *Tetrahedron Lett.* **1997**, *38*, 5819–5820.

[225] D. Rolf, G. R. M. S. Choi, P. M. Myerscough, A. J. Fairbanks, B. M. Skead, C. J. F. Bichard, S. J. Mantell, J. C. Son, G. W. J. Fleet, J. Saunders, D. Brown, *J. Chem. Soc., Chem. Commun.* **1992**, 1605–1607.

[226] M. Cifonelli, J. A. Cifonelli, R. Montgomery, F. Smith, *J. Am. Chem. Soc*. **1955**, *77* 121–125.

[227] I. Lundt, H. Frank, *Tetrahedron* **1994**, *50*, 13285–13298.

[228] a) D. Rolf, G. R. Gray, *J. Am. Chem. Soc*. **1982**, *104*, 35393541; b) D. Rolf, J. A. Bennek, G. R. Gray, *J. Carbohydr. Chem.* **1983**, *2*, 373–383; c) J. A. Bennek, G. R. Gray, *J. Org. Chem.* **1987**, *52*, 892.

[229] G. J. Ewing, M. J. Robins, *Org. Lett.* **1999**, *1*, 635–636.

[230] R. Lazny, A. Nodzewska, *Chem. Rev.* **2010**, *110*, 1386–1434.

[231] R. Fernández, J. M. Lassaletta, *Synlett* **2000**, 1228–1240.

[232] a) A. G. Fallis, I. M. Brinza, *Tetrahedron* **1997**, *53*, 17543–17594; b) G. K. Friestad, *Tetrahedron* **2001**, *57*, 5461–5496.

[233] F. Pautet, P. Nebois, Z. Bouaziz, H. Fillion, *Heterocycles* **2001**, *54*, 1095–1138.

[234] A. Job, C. F. Janeck, W. Bettray, R. Peters, D. Enders, *Tetrahedron* **2002**, *58*, 2253–2329.

[235] K. C. Nicolaou, S. Ninkovic, F. Sarabia, D. Vourloumis, Y. He, H. Vallberg, M. R. V. Finlay, Z. Yang, *J. Am. Chem. Soc*. **1997**, *119*, 7974–7991.

[236] D. Enders, L. Wortmann, R. Peters, *Acc. Chem. Res.* **2000**, *33*, 157–169.

[237] a) R. Brehme, D. Enders, R. Fernandez, J. M. Lassaletta, *Eur. J. Org. Chem*. **2007**, 5629–5660; b) S. Breitler, E. M. Carreira, *J. Am. Chem. Soc.* **2015**, *137*, 5296–5299.

[238] B. Maji, K. Troshin, H. Mayr, *Angew. Chem. Int. Ed.* **2013**, *52*, 11900–11904.

[239] a) T. Severin, H. Lerche, B. Zimmermann, *Chem. Ber*. **1985**, *118*, 4760–4773; b) H. Lerche, T. Severin*, Chem. Ber.* **1978**, *111*, 1195–1209.

[240] E. W. Warnhoff, W. S. Johnson, *J. Am. Chem. Soc.* **1953**, *75,* 494–496.

[241] M. Behforouz, J. L. Bolan, M. S. Flynt, *J. Org. Chem.* **1985**, *50*, 1186–1189.

[242] F. W. Lichtenthaler, T. Weimer, S. Immel, *Tetrahedron: Asymmetry* **2004**, *15*, 2703-2709.

[243] a) M. M. El Sadek, N. S. A. El-Dayem, S. Y. Hassan, M. A. Mostafa, G. A. Yacout, *Molecules* **2014**, *19*, 5163–5190; b) M. A. E. Sallam, O. G. A. Hamid, V. Gossen, G. Raabe, S. Aboulela, *Carbohydrate Res*. **2012**, *361*, 78–82; c) T. Tschamber, H. Rudyk, D. Le Nouën, *Helv. Chim. Acta* **1999**, *82*, 2015–2019.

[244] J. He, Y. –N. Yang, J. Jiang, Z. –M. Feng, P. –C. Zhang, *Org. Lett.* **2014**, *16*, 5714−5717.

[245] M. Koóš, H. S. Moscher, *Collect. Czech. Chem. Commun.* **1985**, 1994–1999.

[246] a) I. S. Young, P. S. Baran, *Nature Chem.* **2009**, *1*, 193–205; b) T. Saloranta, R. Leino, *Synlett* **2015**, *26*, 421–425.

[247] A. P. Tantsyrev, L. V. Kanitskaya, A. V. Rokhin, G. G. Levkovskaya, *Russ. J. Organ. Chem.* **2004**, *40*, 1735–1736.

[248] L. C. Cooper, E. J. Carlson, J. L. Castro, G. C. Chicchi, K. Dinnell, J. Di Salvo, J. M. Elliott, G. J. Hollingworth, M. M. Kurtz, M. P. Ridgill, W. Rycroft, K. –L. Tsao, C. J. Swain, *Bioorg*. *Med. Chem. Lett.* **2002**, *12*, 1759–1762.

[249] D. Alonso, J. Font, R. M. Ortuno, *J. Org. Chem.* **1991**, *56*, 5567–5572.

[250] http://www.sigmaaldrich.com. Based on prices quoted on 03/05/2015.

[251] J. F. Alfaro, T. Zhang, D. P. Wynn, E. L. Karschner, Z. S. Zhou, J. F. Alfaro, T. Zhang, D. P. Wynn, E. L. Karschner, Z. S. Zhou, *Org. Lett.* **2004**, *6*, 3043–3046.

[252] R. N. Monrad, R. Madsen, *J. Org. Chem.* **2007**, *72,* 9782–9785.

[253] S. J. Mantel, P. S. Ford, D. J. Watkin, G. W. J. Fleet, D. Brown, *Tetrahedron* **1993**, *49*, 3343–3358.

[254] G. Bégis, D. E. Cladingboel, L. Jerome, W. B. Motherwell, T. D. Sheppard, *Eur. J. Org. Chem.* **2009**, 1532–1548.

[255] R. Ferndández, C. Gasch, J. –M. Lassaletta, J. –S. Liera, J. Vázquez, *Tetrahedron Lett.* **1993**, *34*, 141–144.

[256] J. Fuentes, M. Angulo, M. A. Pradera*, J. Org. Chem*. **2002**, *67*, 2577–2587.

[257] J. De Villiers, L. Koekemoer, E. Strauss, *Chem. Eur. J*. **2010**, *16*, 10030–10041.

[258] R. W. Foster, C. J. Tame, H. C. Hailes, T. D. Sheppard, *Adv. Synth. Catal.* **2013**, *355*, 2353–2360.

[259] R. W. Foster, L. Benhamou, M. J. Porter, D. –K. Bučar, H. C. Hailes, C. J. Tame, T. D. Sheppard, *Chem. Eur. J.* **2015**, *21*, 6107–6114.

[260] R. W. Foster, D. –K. Bučar, H. C. Hailes, C. J. Tame, T. D. Sheppard, Manuscript in Preparation.

[261] E. J. Rayment, N. Summerhill, E. A. Anderson, *J. Org. Chem.* **2012**, *77*, 7052−7060.

[262] J. D. Sunderhaus, H. Lam, G. B. Dudley, *Org. Lett*. **2003**, *5*, 4571–4573.

[263] S. E. Denmark, R. F. Sweis, *Acc. Chem. Res.* **2002**, *35*, 835–846.

[264] P. Pahari, B. Senapati, D. Mal, *Tetrahedron Lett.* **2004***, 45,* 5109–5112.

[265] G. Strobela, E. Forda, J Woraponga, J.K. Harper, A. M. Arif, D. M. Grant, P. C. W. Fung, R. M. W. Chaud, *Phytochemistry* **2002**, *60*, 179–183.

[266] K. M. Brummond, D. Chen, M. M. Davis, *J. Org. Chem.* **2008**, *73*, 5064–5068.

[267] M. –C. Gutiérrez, R. Furstoss, V. Alphand, *Adv. Synth. Catal.* **2005**, *347*, 1051–1059.

[268] F. C. Mutti, C. S. Fuchs, D. Pressnitz, J. H. Sattler, W. Kroutil, *Adv. Synth. Cat.* **2011**, *353*, 3227–3233.

[269] a) H. Ding, Y. Zhang, M. Bian, W. Yao, C. Ma, *J. Org. Chem*. **2008**, *73*, 578–584; b) J. McNally, J. B. Press, *J. Org. Chem*. **1991**, *56*, 245–251; c) R. H. Schlessinger, T. R. R. Pettus, J. P. Springer, K. Hoogsteen, *J. Org. Chem*. **1994**, *59*, 3246–3247.

[270] M. S. Manna, S. Mukherjee, *Chem. Eur. J.* **2012**, *18*, 15277–15282.

[271] a) J. D. Winkler, K. Oh, S. M. Asselin, *Org. Lett.* **2005**, *7,* 387–389; b) C. Du, L. Li, Y. Li, Z. Xie, *Angew. Chem. Int. Ed*, **2009**, *48*, 7853–7856; c) R. Antonioletti, F. Bonadies, A. Scettri, *Tetrahedron Lett.* **1987**, *28*, 2297–2298; d) J. L. Shamshina, T. S. Snowden, *Tetrahedron Lett.* **2007**, *48*, 3767–3769.

[272] a) R. S. Singh, S. Adachi, F. Tanaka, T. Yamauchi, C. Inui, T. Harada, *J. Org. Chem*. **2008**, *73*, 212–218; b) D. A. Evans, D. M. Barnes, J. S. Johnson, T. Lectka, P. von Matt, S. J. Miller, J. A. Murry, R. D. Norcross, E. A. Shaughnessy, K. R. Campos, *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594; c) A. Sakakura, R. Kondo, Y. Matsumura, M. Akakura, K. Ishihara, *J. Am. Chem. Soc.* **2009**, *131*, 17762–17764.

[273] a) A. Barteselli, S. Parapini, N. Basilico, D. Mommo, A. Sparatore, *Bioorg. Med. Chem.* **2014**, *22*, 5757–5765; b) H. Sun, K. M. Millar, J. Yang, K. Abboud, B. A. Horenstein, *Tetrahedron Lett.* **2000**, *41*, 2801–2804; c) S. Chiba, M. Kitamura, K. Narasaka, *J. Am. Chem. Soc.* **2006**, *128*, 6931–6937.

[274] J. T. Reeves, M. D. Visco, M. A. Marsini, N. Grinberg, C. A. Busacca, A. E. Mattson, C. H. Senanayake, *Org. Lett.* **2015**, *17*, 2442–2445.

[275] E. E. Carlson, L. L. Kiessling, *J. Org. Chem.* **2004**, *69*, 2614–2617.

[276] L. De Luca, G. Giacomelli, A. Porcheddu, *Org. Lett.* **2001**, *3*, 3041–3043.

[277] D. Moffat, C. J. Nichols, D. A. Riley, N. S. Simpkins, *Org. Biomol. Chem.* **2005**, *3*, 2953–2975; b) A. J. Durie, A. M. Z. Slawin, T. Lebl, D. O'Hagan, *Angew. Chem. Int. Ed.* **2012**, *51*, 10086–10088; c) T. Schlaeger, C. Oberdorf, B. Tewes, B. Wuensch, *Synthesis* **2008**, *11,* 1793–1797.

[278] R. K. Henderson, A. P. Hill, A. M. Redman, H. F. Sneddon, *Green Chem.* **2015**, *17*, 945–949.

[279] M. Shi, C. –J. Wang, *J. Chem. Res.* **2004**, *28*, 107–110.

[280] S. W. Brown, P. L. Pauson, *J. Chem. Soc. Perkin Trans. 1* **1990**, 1205–1209.

[281] Y. Hirata, T. Yukawa, N. Kashihara, Y. Nakao, T. Hiyama, *J. Am. Chem. Soc.* **2009**, *131*, 10964–10973.

[282] D. M. Duckworth, S. Lee-Wong, A. M. Z. Slawin, E. H. Smith, D. J. Williams, *J. Chem. Soc. Perkin Trans. 1* **1996**, 815–821.

[283] A. Schaate, P. Roy, T. Preuße, S. J. Lohmeier, A. Godt, P. Behrens, *Chem. Eur. J.* **2011**, *17*, 9320–9325.

[284] A. Rosowsky, R. A. Forsch, C. A. Sibley, C. B. Inderlied, S. F. Queener, *J. Med. Chem.* **2004**, *47*, 1475–1486.

[285] *CrysAlisPro*, Agilent Technologies, Version 1.171.37.34 (release 22-05-2014 CrysAlis171 .NET).

[286] G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *64*, 112–122.

Appendix

The following manuscipts are included in the appendix to this thesis;

1. R. W. Foster, C. J. Tame, H. C. Hailes, T. D. Sheppard, *Adv. Synth. Catal.* **2013**, *355*, 2353–2360. Highly Regioselective Synthesis of Substituted Isoindolinones *via* Ruthenium-Catalyzed Alkyne Cyclotrimerizations

2. M. N. Pennell, R. W. Foster, P. G. Turner, H. C. Hailes, C. J. Tame, T. D. Sheppard, *Chem. Commun.* **2014**, *50*, 1302–1304. Gold Catalysed Synthesis of 3-Alkoxyfurans at Room Temperature

3. R. W. Foster, L. Benhamou, M. J. Porter, D. –K. Bučar, H. C. Hailes, C. J. Tame, T. D. Sheppard, *Chem. Eur. J.* **2015**; *21*, 6107–6114. Irreversible *endo*-Selective Diels–Alder Reactions of Substituted Alkoxyfurans: a General Synthesis of *endo*-Cantharimides

4. R. W. Foster, C. J. Tame, D. –K. Bučar, H. C. Hailes, T. D. Sheppard, *Chem. Eur. J. Manuscript Accepted.* The Sustainable Synthesis of Chiral Tetrahydrofurans *via* the Selective Dehydration of Pentoses

The following files are included in the electronic appendix to this thesis, which can be found on a CD in the inside of the back cover;

1. Computational Supporting Information.

2. The.cif file for *endo*-**330e**.

3. The.cif file for *exo*-**330e**.

4. The.cif file for *anti*-**443e**.

DOI: 10.1002/adsc.201300055

Highly Regioselective Synthesis of Substituted Isoindolinones *via* Ruthenium-Catalyzed Alkyne Cyclotrimerizations

Robert W. Foster,[a] Christopher J. Tame,[b] Helen C. Hailes,[a] and Tom D. Sheppard[a,*]

[a] Department of Chemistry, University College London, Christopher Ingold Laboratories, London, WC1H 0AJ, U.K.
Fax: (+44)-(0)20-7679-7463; phone: (+44)-(0)20-7679-2467; e-mail: tom.sheppard@ucl.ac.uk
[b] GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG12NY, U.K.

Received: January 21, 2013; Revised: May 23, 2013; Published online: August 12, 2013

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300055.

Abstract: (Cyclooctadiene)(pentamethylcyclopentadiene)ruthenium chloride [Cp*RuCl(cod)] has been used to catalyze the regioselective cyclization of amide-tethered diynes with monosubstituted alkynes to give polysubstituted isoindolinones. Notably, the presence of a trimethylsilyl group on the diyne generally led to complete control over the regioselectivity of the alkyne cyclotrimerization. The cyclization reaction worked well in a sustainable non-chlorinated solvent and was tolerant of moisture. The optimized conditions were effective with a diverse range of alkynes and diynes. The 7-silylisoindolinone products could be halogenated, protodesilylated or ring opened to access a range of usefully functionalized products.

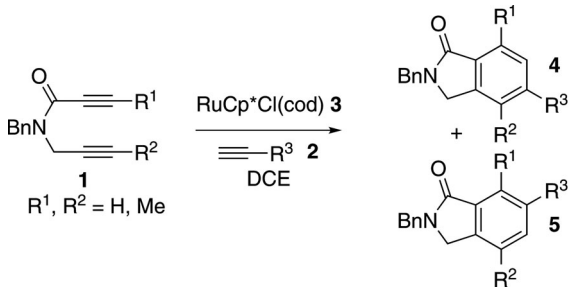
Keywords: alkynes; amide tether; cyclotrimerization; isoindolinones; ruthenium; trimethylsilyl group

Introduction

Substituted isoindolinones have recently generated considerable interest because of their diverse biological activities, including the inhibition of angiogenesis,[1] tumour necrosis factor production,[2] MDM2-p53 protein-protein interactions,[3] hypoxia-inducible factor-1α[4] and histone deacetylase.[5] The majority of existing protocols for isoindolinone synthesis require the construction of a γ-lactam adjacent to a preformed aromatic core.[6] Recent examples include the one-pot transformation of 2-halobenzaldimines into chiral 3-substituted isoindolinones and the Ni-mediated cyclization of *N*-benzoyl aminals in the presence of a stoichiometric Lewis acid.[7,8] However, the inevitable limitation of these approaches is the accessibility of the arene starting material itself. The synthesis of polysubstituted arenes is often non-trivial, frequently requiring numerous steps, the use of protecting group strategies and/or functional group interconversions.

The transition metal-catalyzed [2+2+2] cyclotrimerization of alkynes is emerging as an elegant, atom efficient and convergent approach to the synthesis of highly substituted arenes.[9] The strategy allows for the regioselective synthesis of compounds that would be extremely difficult to make *via* traditional aromatic chemistry. The regioselectivity of a cyclotrimerization is normally controlled by tethering two or three of the alkyne components together, so this strategy is best suited to the synthesis of bicyclic and tricyclic ring systems. This allows for the assembly of substituted multiple-ring aromatic compounds from alkyne precursors in a single step.

Yamamoto and co-workers have previously recognized the potential of alkyne cyclotrimerizations for the synthesis of isoindolinones bearing substituents on the aromatic ring.[10] They reported the cyclization of amide-tethered diynes **1** with monoynes **2** using Cp*RuCl(cod) **3** as the catalyst to give regioisomeric isoindolinones **4** and **5** (Scheme 1). In general the regioselectivity of the cyclotrimerization was poor to moderate, with the exception of a single example bearing a methyl group at R^1. In addition, a significant limitation of this method is the use of 1,2-dichloroethane (DCE) as solvent, a substance which is potentially detrimental to human health and is generally avoided within industry.[11]



Scheme 1. Isoindolinone synthesis as reported by Yamamoto and co-workers.[10]

The aim of this study was to explore the regioselective synthesis of polysubstituted isoindolinones using more industrially viable reaction conditions, to establish the general applicability of the reaction, and to develop the synthetic potential of the cyclized products. On the basis of previously reported cyclizations we envisaged that the introduction of a trimethylsilyl group at R^1 in diyne **1** would direct the regioselectivity of the cyclisation reaction effectively with a broad range of monoynes.[10,12] The arylsilane unit present in the isoindolinone product could then be transformed using standard chemical techniques to access a variety of 7-substituted derivatives.

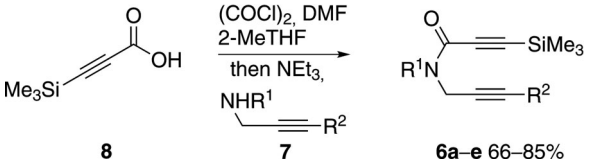
Results and Discussion

Diyne Synthesis

Initially several amide-tethered diynes **6** were prepared by the coupling of propargylic amines **7** with 3-(trimethylsilyl)propiolic acid **8**, *via* the corresponding acid chloride (Scheme 2).[13] Where necessary the corresponding amines were prepared using literature procedures.[14–15]

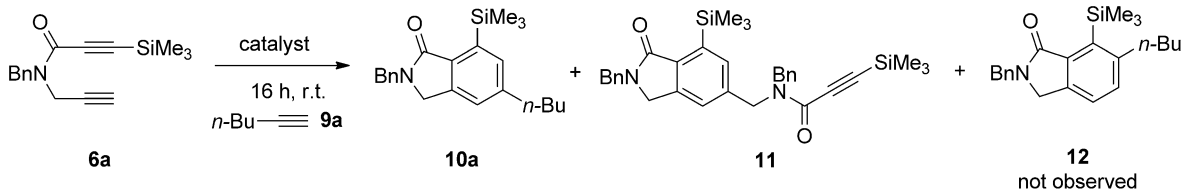
Optimization

Various conditions were screened for the cyclotrimerization of diyne **6a** with 1-hexyne **9a** to form isoindolinone **10a**, and the results are summarized in Table 1. All reactions were conducted for 16 h at which point



Scheme 2. Synthesis of diynes **6a–e**.

Table 1. Optimization of the cyclotrimerization of **6a** and **9a**.



Entry	Solvent	Equivalents of **9a**	Catalyst	Catalyst loading [mol%]	Conversion[a,b] [%]	Ratio **10a**:**11**[a]
1	PhMe[c]	4	$RhCl(PPh_3)_3$	5	<5	–
2	PhMe[c]	4	$Co_2(CO)_8$	10	<5	–
3	CH_2Cl_2[c]	4	Grubbs I	5	5	n.d.
4	DCE[c]	4	Cp*RuCl(cod)	1	5	n.d.
5	neat[d]	4	Cp*RuCl(cod)	1	50	3:2
6	neat[d]	4	Cp*RuCl(cod)	3	100	3:1
7	CPME	4	Cp*RuCl(cod)	3	100	5:1
8	CPME	4	Cp*RuCl(cod)	1	60	4:1
9	CPME	2	Cp*RuCl(cod)	3	100	2:1
10[e]	CPME	4	Cp*RuCl(cod)	3	100	8:1
11[e]	**CPME**	**2**	**Cp*RuCl(cod)**	**3**	**100**	**9:1**
12[e]	CPME	1.1	Cp*RuCl(cod)	3	100	5:2
13[e]	MTBE	2	Cp*RuCl(cod)	3	100	5:1
14[e]	2-MeTHF	2	Cp*RuCl(cod)	3	90	5:1
15[e]	CPME/10% water	2	Cp*RuCl(cod)	3	70	3:1
16	water	4	Cp*RuCl(cod)	3	30	3:1

[a] Determined by analysis of the crude ^1H NMR spectrum.
[b] Conversion of **6a** into **10a** and **11** (determined by crude ^1H NMR without the use of an internal standard).
[c] Solvent dried over activated 4 Å molecular sieves and degassed.
[d] Cp*RuCl(cod) **3** was added to the reaction mixture at 0 °C, which was then allowed to reach room temperature.
[e] Diyne **6a** in CPME was added dropwise over 3 h to a stirring solution of **9a** and **3** in CPME.

conversion and selectivity were determined by analysis of the crude ^{1}H NMR spectrum.

The cyclotrimerization of diyne **6a** and alkyne **9a** was examined using four different literature procedures. Neither $RhCl(PPh_3)_3$ nor $Co_2(CO)_8$ were effective in catalyzing the alkyne cyclotrimerization, with no measurable conversion of diyne **6a** (entries 1 and 2).[16] Treating diyne **6a** with 5 mol% Grubbs' first generation catalyst and 4 equivalents of 1-hexyne **9a** in dried, degassed CH_2Cl_2 resulted in formation of the target isoindolinone **10a** with only 5% conversion (entry 3).[17] Treating diyne **6a** with 1-hexyne **9a** and 1 mol% Cp*RuCl(cod) in dried, degassed DCE also gave isoindolinone **10a**, again with 5% conversion of **6a** (entry 4).[10] Given that the latter procedure gave a similar conversion with a lower catalyst loading, Cp*RuCl(cod) was selected for subsequent optimization.

Interestingly, treating diyne **6a** with 1-hexyne **9a** and 1 mol% Cp*RuCl(cod) with no solvent (neat) at 0 °C gave isoindolinone **10a** with a 50% conversion (entry 5). This suggests that using DCE as a solvent for this reaction is actually detrimental. In addition to the desired isoindolinone **10a**, dimer **11** was also formed as a significant by-product.[12]

Crucially, regioisomeric cyclotrimerization product **12** was not observed at all in the crude ^{1}H NMR spectrum. The reaction under neat conditions reached completion within 16 h when 3 mol% of catalyst **3** was used, and with a significant reduction in the proportion of homo-coupled product **11** produced (entry 6).

We were interested in using cyclopentyl methyl ether (CPME) as a solvent for this cyclization as it has been recently established as a safer and more environmentally benign alternative to many traditional organic solvents.[18] As shown in entry 7, when the reaction was conducted in CPME with 3 mol% of catalyst **3**, diyne **6a** was completely consumed within 16 h and an improved selectivity for the cross-coupled product **10a** was observed. By comparison, the same reaction using only 1 mol% catalyst resulted in a comparable level of selectivity, but a lower conversion (entry 8). Reducing the number of equivalents of 1-hexyne **9a** to two resulted in the complete consumption of diyne **6a** but also a significantly increased level of homo-coupling.

In an attempt to minimise the formation of dimer **11**, diyne **6a** was added dropwise over 3 h to a stirring solution of monoyne **9a** and catalyst **3**,[19] and this proved to be highly effective (entry 10). When using the 3-hour dropwise addition it was possible to reduce the number of equivalents of 1-hexyne **9a** from four to two with no increase in homo-coupling (entry 11). A further reduction to 1.1 equivalents of 1-hexyne **9a** did result in increased homo-coupling, but target isoindolinone **10a** was still the major product (entry 12). The cyclization of **6a** and **9a** was also effective when 2-MeTHF or MTBE were used as solvents, but in both cases a greater degree of homo-coupling of **6a** was observed than with CPME (entries 13 and 14). The reaction proved to be relatively water tolerant, with a significant conversion and a reasonable selectivity observed when the reaction was conducted in the presence of 10% water (entry 15). Cyclization was even observed when the reaction was conducted in water as solvent (entry 16). This is important as it could enable the extension of the reaction to aqueous conditions for reactions of water-soluble substrates.

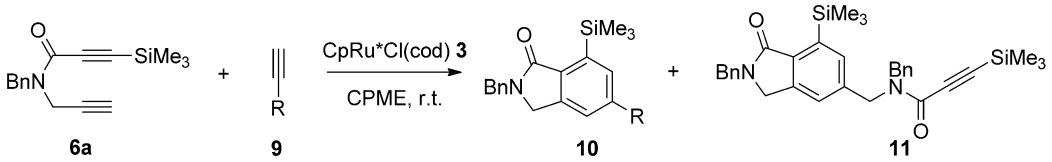
Following the optimization study the conditions described in entry 11 were taken as the "optimized" cyclization conditions as they required a reduced excess of monoyne and minimized the formation of dimer **11**. Crucially this protocol did not require the CPME solvent to be either degassed or dried. This, together with the environmental benefits of CPME, makes this reaction a very practical method for the synthesis of isoindolinones. Dimer **11** could be readily separated from the desired product by flash column chromatography, and the optimized conditions described in entry 11 gave the target isoindolinone **10a** in 81% isolated yield (Table 2, entry 1). This reaction was also scaled up to a 500-mg scale and isoindolinone **10a** was isolated in 66% yield (428 mg product).

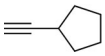
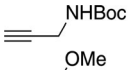
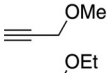
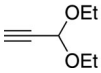
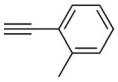
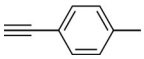
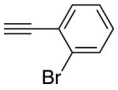
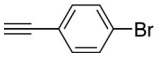
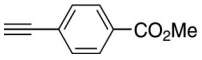
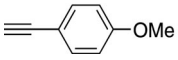
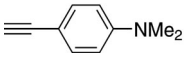
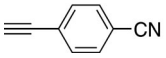
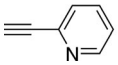
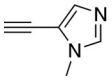
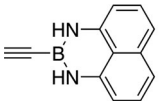
Monoyne Scope

The cyclization of **6a** was then examined with a variety of monoynes using the optimized conditions described above to determine how robust the reaction was for a range of different substrates. Diyne **6a** cyclized with a wide range of monynes **9** as detailed in Table 2. Crucially, no evidence for the formation of regioisomeric isoindolinones was observed in any of the cyclization reactions. Alkyl monoynes **9a–e** cyclized efficiently with **6a** to give the corresponding isoindolinones **10a–e** in good isolated yield (entries 1–5, 66–83%). Little formation of the undesired dimer **11** was observed, except in the reaction of *tert*-butylacetylene **9b**, presumably due to high steric crowding about the monoalkyne. Carbamate **9f** cyclized with **6a** to give **10f** in reasonable yield and with modest levels of homo-coupling (entry 6).

Ether **9g** and acetal **9h** both underwent cyclotrimerization with **6a**, but with the formation of significant quantities of dimer **11**. Propargylic alcohol **9i** and methoxyacetylene **9j** both failed to cyclize with diyne **6a**, with only starting material being recovered in both cases. In addition to aliphatic monoynes, diyne **6a** cyclized effectively with a broad range of aromatic monoynes. Electron-rich (entries 12, 13, 17 and 18), electron-poor (entry 16) and sterically hindered substrates (entries 12 and 14) could all be tolerated and products

Table 2. Reaction of diyne **6a** with a selection of monoynes **9**.[a]

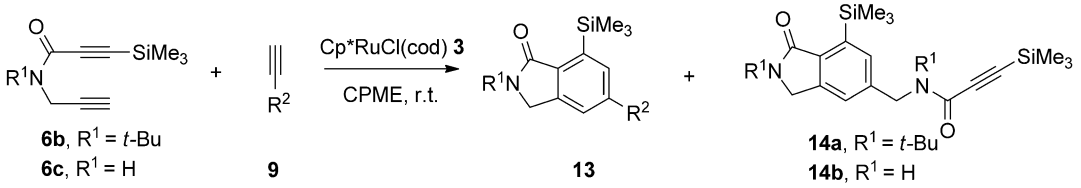


Entry	Alkyne **9**		**3** [mol%]	Time [h]	Product **10**	Yield of **10** [%][b]	Ratio **10**:**11**[c]
1	*n*-Bu	**9a**	3	16	**10a**	81	9:1
2	*t*-Bu	**9b**	3	16	**10b**	66	2:1
3		**9c**	3	16	**10c**	81	9:1
4		**9d**	3	16	**10d**	81	6:1
5	$(CH_2)_3Cl$	**9e**	3	16	**10e**	83	8:1
6		**9f**	5	24	**10f**	63	2:1
7		**9g**	3	16	**10g**	56	3:2
8		**9h**	3	24	**10h**	43	4:5
9		**9i**	3	16	–	0	–
10	OMe	**9j**	3	16	–	0	–
11	Ph	**9k**	4	24	**10k**	83	6:1
12		**9l**	3	16	**10l**	93	>10:1
13		**9m**	4	24	**10m**	83	6:1
14		**9n**	3	16	**10n**	80	8:1
15		**9o**	3	24	**10o**	83	5:1
16		**9p**	3	24	**10p**	79	5:1
17		**9q**	5	24	**10q**	79	6:1
18		**9r**	10	24	**10r**	79	7:1
19		**9s**	3	16	–	0	-
20		**9t**	20	24	**10t**	50	2:1
21		**9u**	3	16	**10u**	0	-
22		**9v**	5	24	**10v**	55	3:1

[a] *Reaction conditions:* A solution of **6a** in CPME was added dropwise to a stirring solution of **9** and **3** in CPME over 3 h at room temperature.
[b] Isolated yield.
[c] Determined by the analysis of crude ^{1}H NMR spectra.

were isolated in good yields (79–93%) with low levels of diyne homo-coupling. For most of these examples longer reaction times (up to 24 h), and in some cases higher catalyst loadings, were required to drive the reaction to completion. However the reactions with *ortho*-substituted arylacetylenes **9l** and **9n** reached

Table 3. Cyclizations involving diynes with different *N*-substituents.[a]



6b, R^1 = *t*-Bu
6c, R^1 = H
9
13
14a, R^1 = *t*-Bu
14b, R^1 = H

Entry	R^1	R^2	**3** [mol%]	Time [h]	Product **13**	Yield of **13** [%][b]	Ratio of **13**:**14**[c]
1	*t*-Bu **6b**	*n*-Bu **9a**	3	16	**13a**	84	10:1
2	*t*-Bu **6b**	Ph **9k**	4	24	**13b**	89	>10:1
3	*t*-Bu **6b**	*o*-tolyl **9l**	3	16	**13c**	94	>10:1
4	H **6c**	*n*-Bu **9a**	10	24	**13d**	51 (90%[d])	2:1
5	H **6c**	*o*-tolyl **9l**	10	24	**13e**	62 (90%[d])	7:1

[a] *Reaction conditions:* a solution of **6** in CPME was added dropwise to a stirring solution of **9** and **3** in CPME over 3 h at room temperature.
[b] Isolated yield.
[c] Determined by the analysis of crude ^{1}H NMR spectra.
[d] Conversion of diyne **6** to **13**/**14** (determined by crude ^{1}H NMR without the use of an internal standard).

completion within 16 h with only 3 mol% of catalyst **3** (entries 12 and 14). Monoyne **9l** also cyclized with exceptionally high selectivity for the cross-coupled product **10l** over dimer **11**, whereas *ortho*-bromo alkyne **9n** gave a slightly lower selectivity. Although Yamamoto et al. have reported the [2+2+2]cycloaddition of an electron-deficient nitrile and an amide-tethered diyne to give a pyridine,[20] in our reaction nitrile **9s** failed to cyclize with **6a** to form any product *via* reaction of either the alkyne or the nitrile (entry 19). Only a limited quantity of **11** (~10%) was formed in this reaction suggesting that **9s** may inhibit the catalyst. Heterocycle-containing alkyne **9t** cyclized effectively with **6a** to give the corresponding 2-pyridyl derivative **10t** in a moderate 50% yield (entry 20). In contrast *N*-methylimidazole **9u** failed to cyclize with **6a**, with unreacted starting material being recovered (entry 21). Alkyne **9v** cyclized with **6a** to give boramide **10v** in reasonable yield (entry 22).[21]

Diyne Scope

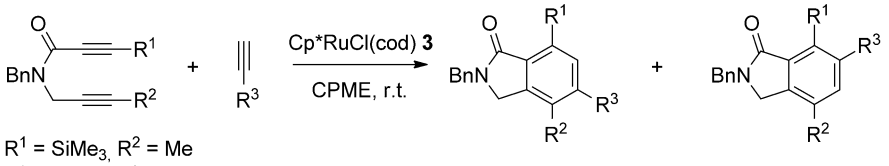
The cyclization of amide-tethered diynes bearing different *N*-substituents was examined and the results are summarized in Table 3. *N*-*t*-Bu diyne **6b** proved to be an excellent substrate for the synthesis of 5,7-substituted isoindolinones. Treatment of **6b** with 1-hexyne **9a** under the optimized reaction conditions gave isoindolinone **13a** in 84% yield with little formation of the dimer **14a** (entry 1). The cyclization of **6b** with **9k** required 4 mol% **3** and 24 h to reach completion, giving isoindolinone **13b** in 89% yield (entry 2). The reaction of **6b** with 2-ethynyltoluene **9l** proceeded in 94% yield without an elevated reaction time or an increased loading of catalyst **3**, and also occurred with very little formation of dimer **14a** (entry 3).

The *N*-H diyne **6c** proved less effective for the synthesis of isoindolinones, with the cyclization of **6c** and 1-hexyne **9a** requiring 10 mol% Cp*RuCl(cod) **3** and 24 h to achieve a 90% conversion of diyne **6c** (entry 4). Isoindolinone **13d** was only formed in modest yield (51%) and significant formation of dimer **14b** was observed. Under the same conditions the cyclization of 2-tolylacetylene **9l** and N-*H* diyne **6c** gave the desired isoindolinone **13e** in a slightly higher yield with 90% conversion. Again, the reaction with 2-ethynyltoluene **9l** proved to be unusually selective, with **13e** and **14b** formed in the ratio 7:1 (entry 5). The lack of a sterically bulky *N*-substituent is presumably responsible for both the reduced reactivity of *N*-H diyne **6c** with monoynes and the high level of diyne homo-coupling observed in these reactions.

The cyclization of amide-tethered diynes bearing different alkyne substituents was also explored (Table 4). With doubly substituted diynes **6d** and **6e**, no homo-coupling of the diyne was observed and dropwise addition of the diyne to the reaction was unnecessary (entries 1–3). With 10 mol% of Cp*RuCl(cod), methyl-substituted diyne **6d** cyclized with 1-hexyne **9a** to form a 9:1 mixture of regioisomeric isoindolinones **15a** and **16a** (entry 1).

Ethyl-substituted diyne **6e** reacted with 1-hexyne **11a** with lower regioselectivity, giving a 2:1 mixture of isoindolinones **15b** and **16b** (entry 2). However, diyne **6e** cyclized with 2-ethynyltoluene **9l**, to give a 5:1 mixture of isoindolinones **15c** and **16c** (entry 3). Interestingly, the presence of diastereotopic benzylic protons in the ^{1}H NMR spectrum suggests that isoindolinone

Table 4. Cyclizations involving diynes with different alkyne substitutents.[a]



6d, R^1 = $SiMe_3$, R^2 = Me
6e, R^1 = $SiMe_3$, R^2 = Et
6f, R^1 = Me, R^2 = H

9

15

16

Entry	Diyne **6**	R^1	R^2	R^3	**3** [mol%]	Time [h]	Isolated products	Yield of (**15**+**16**) [%][b]	Ratio of **15**:**16**[c]
1	**6d**	$SiMe_3$	Me	*n*-Bu **9a**	10	24	**15a/16a**	69	9:1
2	**6e**	$SiMe_3$	Et	*n*-Bu **9a**	10	24	**15b/16b**	57	2:1
3	**6e**	$SiMe_3$	Et	*o*-tolyl **9l**	10	24	**15c/16c**	73	5:1
4[d]	**6f**	Me	H	*n*-Bu **9a**	3	16	**15d**[e]	85	>20:1
5[d]	**6f**	Me	H	*o*-tolyl **9l**	3	16	**15e**	94	>20:1

[a] *Reaction conditions:* A solution of **6** in CPME was added to a stirring solution of **9** and **3** in CPME over 1 min at room temperature.
[b] Isolated yield.
[c] Determined by the analysis of crude ^{1}H NMR spectra.
[d] Diyne **6f** in CPME was added dropwise over 3 h to a solution of **9** and **3** in CPME.
[e] Evidence of limited homo-coupling of **6f** was observed in the crude ^{1}H NMR spectrum.

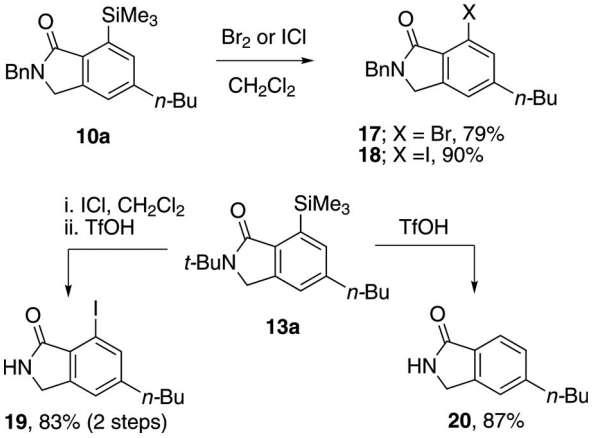
15c is a chiral molecule, presumably due to restricted rotation about the hindered biaryl unit.

The dependence of the cyclotrimerization on an $SiMe_3$ regiodirecting group was also investigated. Diyne **6f** with a terminal methyl substituent reacted with 1-hexyne **9a** under the optimized cyclization conditions to give isoindolinone **15d** in 85% yield (entry 4). Crucially, there was no trace of the regioisomeric isoindolinone **16d** by crude ^{1}H NMR. Similarly, diyne **6f** cyclized with 2-ethynyl toluene **9l** to give isoindolinone **15e** in 94% yield, with no evidence for the formation of regioisomer **16e** (entry 5).

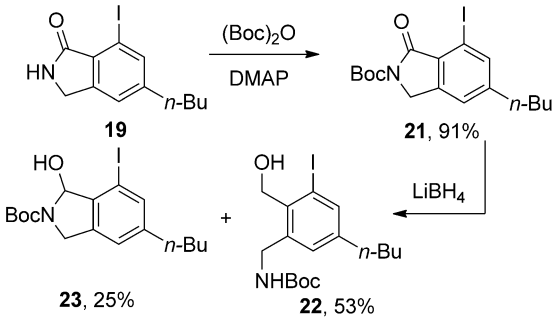
Functional Group Manipulation of Cyclized Products

Conversion of the cyclized isoindolinone products into a number of synthetically interesting motifs was examined. Isoindolinone **10a** was converted to aryl halides **17** and **18**, in 79% and 90% yields, respectively, *via* an *ipso* substitution of the silyl group (Scheme 3).[22] Treatment of *N*-*t*-butylisoindolinone **13a** with triflic acid resulted in a simultaneous deprotection of the lactam and protodesilylation within 30 min to give *N*-H isoindolinone **20** in good yield.[23] Alternatively, treatment of **13a** with iodine monochloride followed by deprotection with triflic acid gave 7-iodoisoindolinone **19** in 83% yield. Thus, an *N*-*t*-Bu diyne can be used as an indirect method for the synthesis of *N*-H isoindolinones *via* this acid-mediated deprotection.

It was also possible to access a tetrasubstituted monocyclic benzene. Treatment of *N*-H isoindolinone



Scheme 3. Synthesis of usefully functionalized isoindolinones.



Scheme 4. Synthesis of a tetrasubstituted benzene ring.

19 with di-*tert*-butyl dicarbonate gave *N*-Boc isoindolinone **21**, which could be reduced with lithium borohydride to form *N*-Boc protected amino alcohol **22**,

together with cyclic aminol **23**, in a combined yield of 78% (Scheme 4). The preparation of mono-cyclic substituted arenes *via* tethered alkyne cyclotrimerizations has little precedent and such systems are somewhat difficult to access *via* traditional aromatic substitution reactions, highlighting the value of this strategy.[24]

Conclusions

In summary, we have demonstrated the regioselective synthesis of polysubstituted isoindolinones *via* the Cp*RuCl(cod)-catalyzed cyclotrimerization of amide-tethered diynes and monoynes. This cyclization is effective with a wide range of structurally diverse monoynes and was demonstrated to work with a variety of different diynes. We have also demonstrated that the cyclization products could be converted into a range of functionalized isoindolinones and a tetrasubstituted benzene derivative.

Experimental Section

Full experimental details are provided in the Supporting Information.

Cp*RuCl(cod)-Catalyzed Cyclization of a Diyne and a Monoyne

A solution of **6a** (500 mg, 1.86 mmol) in CPME (11 mL) was added dropwise over 3 h to a stirring solution of 1-hexyne **9a** (0.43 mL, 300 mg, 3.7 mmol) and Cp*RuCl(cod) (21 mg, 3 mol%) in CPME (7.7 mL) at room temperature. The reaction mixture was stirred for a further 13 h before being filtered through a silica pad, eluting with ethyl acetate. The solvent was removed under vacuum to give the crude product, which was purified by flash column chromatography (13:1 petrol:ethyl acetate) to give 2-benzyl-5-butyl-7-(trimethylsilyl)isoindolin-1-one **10a**; yield: 428 mg (1.22 mmol, 66%); R_f = 0.36 (6:1 petrol:ethyl acetate); IR (film): ν_{max} = 2955 (m, C–H), 2930 (m, C–H), 1688 (s, C=O), 1454 (m), 1409 cm^{-1} (m); ^1H NMR (600 MHz, DMSO-d_6): δ = 7.34–7.21 (7H, m, Ar*H*), 4.68 (2H, s, CH_2N), 4.24 (2H, s, CH_2N), 2.60 (2H, t, J = 7.7, $ArCH_2CH_2$), 1.51, (2H, m, $ArCH_2CH_2$), 1.26 (2H, m, CH_2CH_3), 0.83 (3H, t, J = 7.4, CH_2CH_3), 0.34 [9H, s, $Si(CH_3)_3$]; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.5, 144.8, 142.1, 137.7, 136.9, 134.3, 134.0, 128.6, 127.6, 127.2, 123.7, 48.9, 45.4, 35.1, 33.2, 21.8, 13.7, −0.4; HR-MS (EI^+): m/z = 351.2011 $[M]^+$, $C_{22}H_{29}ONSi$ requires 351.2013.

Acknowledgements

This work was supported by the Engineering and Physical Sciences Research Council (Advanced Research Fellowship EP/E052789/1), together with GlaxoSmithKline (Industrial CASE Award) and the UCL PhD program in Drug Discovery. We would also like to acknowledge Simon Peace (GSK) for helpful discussions.

References

[1] F. A. Luzzio, A. V. Mayorov, S. S. W. Ng, E. A. Kruger, W. D. J. Figg, *J. Med. Chem.* **2003**, *46*, 3793–3799.
[2] G. W. Muller, R. Chen, S. Y. Huang, L. G. Corral, L. M. Wong, R. T. Patterson, Y. Chen, G. Kaplan, D. I. Stirling, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1625–1630.
[3] A. F. Watson, J. Liu, K. Bennaceur, C. J. Drummond, J. A. Endicott, B. T. Golding, R. J. Griffin, K. Haggerty, X. Lu, J. M. McDonnell, D. R. Newell, M. E. M. Noble, C. H. Revill, C. Riedinger, Q. Xu, Y. Zhao, J. Lunec, I. R. Hardcastle, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5916–5919.
[4] M. Uno, H. S. Ban, H. Nakamura, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3166–3169.
[5] S. Lee, C. Shinji, K. Ogura, M. Shimizu, S. Maeda, M. Sato, M. Yoshida, Y. Hashimoto, H. Miyachi, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4895–4900.
[6] a) S. Das, D. Addis, L. R. Knöpke, U. Bentrup, K. Junge, A. Brückner, M. Beller, *Angew. Chem.* **2011**, *123*, 9346–9350; *Angew. Chem. Int. Ed.* **2011**, *50*, 9180–9184; b) J. W. Wrigglesworth, B. Cox, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Org. Lett.* **2011**, *13*, 5326–5329; c) A. Bubar, P. Estey, M. Lawson, S. Eisler, *J. Org. Chem.* **2012**, *77*, 1572–1578; d) C. Petronzi, S. Collarile, G. Croce, R. Filosa, P. De Caprariis, A. Peduto, L. Palombi, V. Intintoli, A. Di Mola, A. Massa, *Eur. J. Org. Chem.* **2012**, 5357–5365; e) L. Shi, L. Hu, J. Wang, X. Cao, H. Gu, *Org. Lett.* **2012**, *14*, 1876–1879.
[7] M. Fujioka, T. Morimoto, T. Tsumagari, H. Tanimoto, Y. Nishiyama, K. Kakiuchi, *J. Org. Chem.* **2012**, *77*, 2911–2923.
[8] D. M. Shacklady-McAtee, S. Dasgupta, M. P. Watson, *Org. Lett.* **2011**, *13*, 3490–3593.
[9] a) Y. Yamamoto, *Curr. Org. Chem.* **2005**, *9*, 503–519; b) N. Agenet, O. Buisine, F. Slowinski, V. Gandon, C. Aubert, M. Malacria, *Org. React.* **2007**, *68*, 1–302; c) W. Hess, J. Treutwein, G. Hilt, *Synthesis* **2008**, 3537–3562; d) L. Zhou, S. Li, K.-i. Kanno, T. Takahashi, *Heterocycles* **2010**, *80*, 725–738; e) P. A. Inglesby, P. A. Evans, *Chem. Soc. Rev.* **2010**, *39*, 2791–2805; f) R. Hua, M. V. A. Abrenica, P. Wang, *Curr. Org. Chem.* **2011**, *15*, 712–729; g) N. Weding, M. Hapke, *Chem. Soc. Rev.* **2011**, *40*, 4525–4538; h) G. Domínguez, J. Pérez-Castells, *Chem. Soc. Rev.* **2011**, *40*, 3430–3444; i) M. R. Shaaban, R. El-Sayed, A. H. M. Elwahy, *Tetrahedron* **2011**, *67*, 6095–6130; j) Y. Shibata, K. Tanaka, *Synthesis* **2012**, *44*, 323–350; k) D. L. J. Broere, E. Ruijter, *Synthesis* **2012**, *44*, 2639–2672.
[10] Y. Yamamoto, K. Kinpara, T. Saigoku, H. Nishiyama, K. Itoh, *Org. Biomol. Chem.* **2004**, *2*, 1287–1294.
[11] a) R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, A. D. Curzons, *Green Chem.* **2011**, *13*, 854–862; b) T. Laird, *Org. Process Res. Dev.* **2012**, *16*, 1–2.
[12] Y. Yamamoto, R. Ogawa, K. Itoh, *Chem. Commun.* **2000**, 549–550.

[13] T. Hamada, D. Suzuki, H. Urabe, F. Sato, *J. Am. Chem. Soc.* **1999**, *121*, 7342–7344.
[14] W. Hess, J. W. Burton, *Chem. Eur. J.* **2010**, *16*, 12303–12306.
[15] A. Nudelman, Y. Binnes, N. Shmueli-Broide, Y. Odessa, J. P. Hieble, A. C. Sulpizio, *Arch. Pharm. Pharm. Med. Chem.* **1996**, *329*, 125–132.
[16] a) B. Witulski, T. Stengel, *Angew. Chem.* **1999**, *111*, 2521–2524; *Angew. Chem. Int. Ed.* **1999**, *38*, 2426–2430; b) B. Witulski, A. Zimmermann, *Synlett* **2002**, 1855–1859; c) B. Witulski, C. Alayrac, *Angew. Chem.* **2002**, *114*, 3415–3418; *Angew. Chem. Int. Ed.* **2002**, *41*, 3281–3284; d) C. Ester, A. Maderna, H. Pritzkow, W. Siebert, *Eur. J. Inorg. Chem.* **2000**, 1177–1184.
[17] B. Witulski, T. Stengel, J. M. Fernández-Hernández, *Chem. Commun.* **2000**, 1965–1966.
[18] K. Watanabe, N. Yamagiwa, Y. Torisawa, *Org. Process Res. Dev.* **2007**, *11*, 251–258.
[19] S. Kezuka, S. Tanaka, T. Ohe, Y. Nakaya, R. Takeuchi, *J. Org. Chem.* **2006**, *71*, 543–552.
[20] Y. Yamamoto, K. Kinpara, T. Saigoku, H. Takagashi, S. Okuda, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2005**, *127*, 605–613.
[21] L. Iannazzo, K. P. C. Vollhardt, M. Malacria, C. Aubert, V. Gandon, *Eur. J. Org. Chem.* **2011**, 3283–3292.
[22] a) J. Clayden, L. Vallverdú, J. Clayton, M. Helliwell, *Chem. Commun.* **2008**, 561–563; b) S. L. MacNeil, M. Gray, D. G. Gusev, L. E. Briggs, V. Snieckus, *J. Org. Chem.* **2008**, *73*, 9710–9719.
[23] G. López-Valdez, S. Oliguín-Uribe, L. D. Miranda, *Tetrahedron Lett.* **2007**, *48*, 8285–8289.
[24] a) G. Chouraqui, M. Petit, C. Aubert, M. Malacria, *Org. Lett.* **2004**, *6*, 1519–1521; b) Y. Yamamoto, J.-I. Ishii, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2004**, *126*, 3712–3713.

ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Gold catalysed synthesis of 3-alkoxyfurans at room temperature†

Cite this: *Chem. Commun.*, 2014, **50**, 1302

Received 29th October 2013,
Accepted 11th December 2013

DOI: 10.1039/c3cc48290a

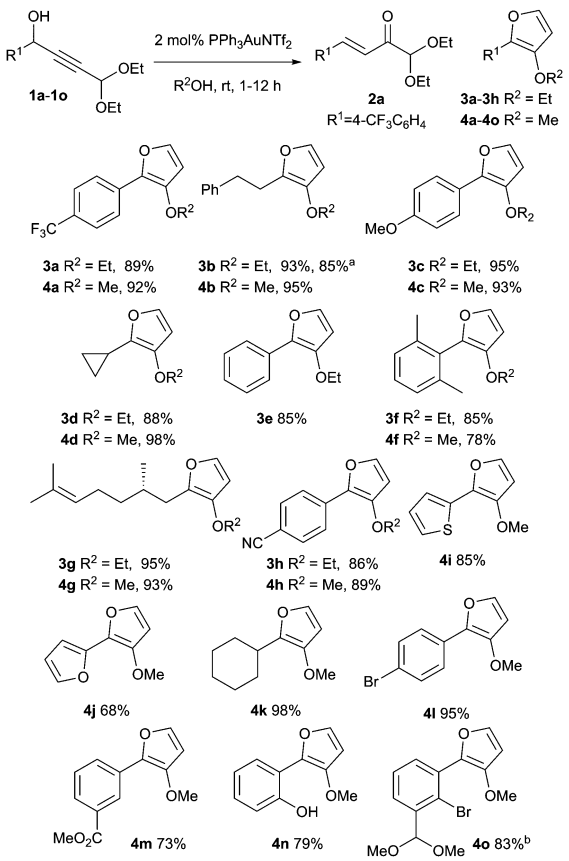
www.rsc.org/chemcomm

Matthew N. Pennell,[a] Robert W. Foster,[a] Peter G. Turner,[b] Helen C. Hailes,[a] Christopher J. Tame[b] and Tom D. Sheppard*[a]

Synthetically important 3-alkoxyfurans can be prepared efficiently *via* treatment of acetal-containing propargylic alcohols (obtained from the addition of 3,3-diethoxypropyne to aldehydes) with 2 mol% gold catalyst in an alcohol solvent at room temperature. The resulting furans show useful reactivity in a variety of subsequent transformations.

Furans are important structural motifs which appear in a wide array of natural products, biologically active compounds and pharmaceuticals.[1] They also have potential uses in the construction of conjugated polymers for applications such as organic electronics.[2] As a consequence, the synthesis of polysubstituted furans has attracted considerable interest. Recent synthetic approaches have included a number of transition-metal catalysed cyclisation reactions[3] mediated by a variety of catalysts[4–8] including systems based on palladium,[4] rhodium,[5] ruthenium[6] and silver.[7] Over the past few years, the use of homogeneous gold catalysts for facilitating the addition of nucleophiles to carbon–carbon multiple bonds has emerged as a very powerful synthetic method[9] and a number of gold-catalysed approaches to the synthesis of heterocyclic aromatic rings,[10] including simple furans,[11] have been reported. Simple 3-alkoxyfurans such as 3-methoxyfuran are highly electron rich systems which show useful reactivity,[12] and have found application in natural product synthesis[13] as well as in the construction of polysubstituted tetrahydrofurans.[14] However, the chemistry of more complex 3-alkoxyfurans has not been widely explored, largely as a consequence of their synthetic inaccessibility.[15] Herein, we describe a gold-catalysed method for the synthesis of a wide variety of 3-alkoxyfurans from readily available propargylic alcohols, *via* a process that allows straightforward variation of substituents both on the furan ring and the alkoxy group.

We have recently reported that the gold-catalysed rearrangement of propargylic alcohols to enones (the Meyer–Schuster rearrangement) proceeds at room temperature in toluene, in the presence of a small amount of alcohol additive (MeOH or EtOH).[16] During the course of our study into the scope of this reaction, we observed that attempted rearrangement of acetal-containing propargylic alcohol **1a** (Scheme 1, R^1 = 4-$CF_3C_6H_4$)



Scheme 1 Gold-catalysed synthesis of 3-ethoxyfurans and 3-methoxyfurans. [a] 600 mg scale reaction. [b] Clean conversion of the aldehyde in propargylic alcohol **1o** into the dimethylacetal occurred under the reaction conditions.

[a] *Department of Chemistry, University College London, 20 Gordon St, London, WC1H 0AJ, UK. E-mail: tom.sheppard@ucl.ac.uk; Fax: +44 (0)7679 7463; Tel: +44 (0)7679 2467*

[b] *GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts, SG1 2NY, UK*

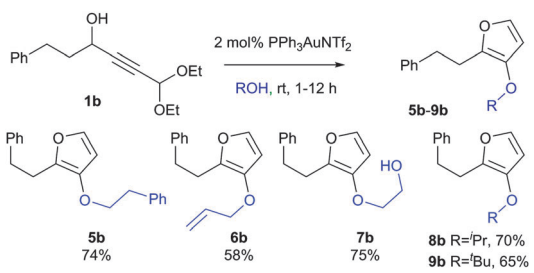
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data for all compounds and ^{1}H and ^{13}C NMR spectra for novel compounds. See DOI: 10.1039/c3cc48290a

gave a mixture of the expected enone **2a** and 3-ethoxyfuran **3a**, where the alcohol additive had become incorporated.[17] Given the importance of polysubstituted furans in a wide variety of applications, we sought to optimise this transformation.[18] Pleasingly in ethanol furan **3a** was formed in 89% yield with complete selectivity. With these optimised conditions in hand, the synthesis of a wide range of 3-ethoxyfurans and 3-methoxyfurans was then explored. High yields (68–98%) of the corresponding furans **3** and **4** were obtained with a selection of propargylic alcohols **1a–1o**. A wide range of aromatic groups can be incorporated at the 2-position of the furan ring, including electron deficient (**1a**, **1h**, **1m**), electron rich (**1c**, **1n**) and sterically encumbered (**1f**) benzene rings, as well as thiophene (**1i**) and furan (**1j**) rings. Propargylic alcohols containing aliphatic groups were also smoothly converted into the corresponding 2-alkyl furans (**1b**, **1d**, **1g**, **1k**). When methanol was used as the reaction solvent, direct solvolysis to generate the 3-methoxyfurans **4** occurred selectively over formation of 3-ethoxyfurans **3**, which could potentially occur *via* incorporation of an ethoxy group derived from the acetal group. Many functional groups including an alkene (**1g**), a nitrile (**1h**), a halide (**1l**), an ester (**1m**), and even a free phenol (**1n**) were compatible with the reaction. In the case of the aldehyde containing substrate **1o**, concomitant formation of the corresponding dimethylacetal **4o** was observed. The synthesis of furan **3b** was performed on a 600 mg scale without difficulty to give the alkyl furan in 85% yield.

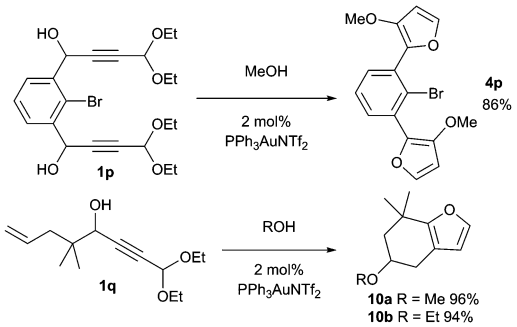
The synthesis of more complex 3-alkoxyfurans was then explored, by incorporation of other alcohols in the furan formation reaction (Scheme 2). Primary (**5b**, **6b**, **7b**), secondary (**8b**) and tertiary (**9b**) alcohols were incorporated efficiently, including functionalised examples such as allyl alcohol (**6b**) and ethylene glycol (**7b**).

It was also possible to construct a conjugated bis-(3-alkoxy-2-furyl)benzene **4p** in excellent yield by gold-catalysed reaction of bis-propargylic alcohol **1p** with MeOH (Scheme 3). The conjugated triaryl unit in **4p** is reminiscent of the oligofuran systems currently being investigated for a variety of applications in organic electronics.[2] Interestingly, propargylic alcohol **1q** containing a nearby alkene unit underwent tandem alcohol addition/ene-yne cyclisation to give fused cyclohexylfurans **10** in excellent yield, with incorporation of the alcohol on the cyclohexane ring. This provides a rapid assembly of the fused furan–cyclohexane motif present in the terpene natural product furadysin.[19]

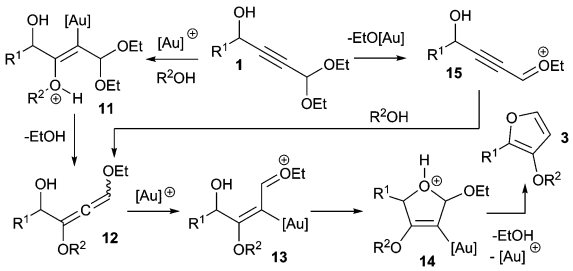
Appropriate control experiments[18] were performed to demonstrate that the gold catalyst was required for the furan



Scheme 2 Incorporation of different alcohols in the 3-alkoxyfuran formation reaction with **1b**.



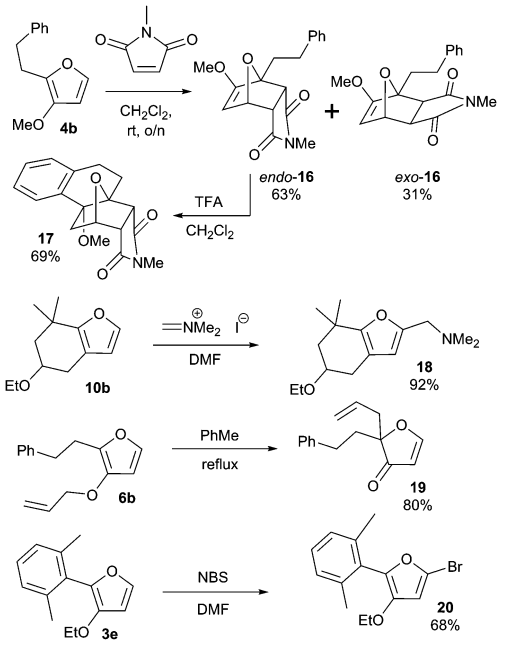
Scheme 3 Synthesis of polycyclic furans.



Scheme 4 Possible mechanism for the gold-catalysed conversion of propargylic alcohols **1** to furans **3**.

formation, and that the reaction was unlikely to be catalysed by Brønsted acid (Tf_2NH)[20] or silver salts ($AgNTf_2$).[16b,21] The furan formation reaction potentially proceeds *via* regioselective gold-catalysed addition of the alcohol to the alkyne to generate vinyl gold intermediate **11** (Scheme 4). Loss of ethanol can then lead to allenyl ether **12** which can undergo further activation by gold to give oxonium ion **13**. Oxonium ion **13** can then be attacked by the nearby alcohol to generate dihydrofuran intermediate **14** which will evolve to the furan **3** after protodeauration and loss of ethanol. An alternative pathway which proceeds *via* Lewis-acid activation of the acetal to generate oxonium ion **15**, followed by conjugate addition of the alcohol to give **12**, can also be envisaged. However, this seems less likely given the fact that the furan formation does not readily occur in the presence of a simple Brønsted acid catalyst.[18]

The electron-rich 3-alkoxyfurans are highly reactive, and care should be taken during the isolation of these compounds in order to prevent decomposition of the products *via* atmospheric oxidation.[18] The reactivity of these furan systems can nevertheless be readily harnessed in a variety of other useful transformations (Scheme 5). Furan **4b** readily underwent a Diels–Alder reaction with *N*-methylmaleimide at room temperature to generate the cycloadduct **16** as a 2 : 1 mixture of separable stereoisomers in excellent overall yield (94%). Treatment of the major diastereoisomer with TFA led to stereoselective cyclisation to give the polycyclic ether **17** in 69% yield. Cyclohexyl fused furan **10b** gave tertiary amine **18** in 92% yield upon reaction with Eschenmoser's salt.[12a] We were also able to promote Claisen rearrangement[22] of the allyloxyfuran **6b** by heating at reflux in toluene to generate 2,2-disubstituted 3-furanone **19** in 80% yield. Electrophilic bromination[23] of furan **3e** proceeded in 75% yield



Scheme 5 Selected reactions of the furan products.

to give bromide **20**, providing a useful building block for cross-coupling reactions.

In summary, we have developed a mild gold-catalysed method for the formation of synthetically useful 3-alkoxyfurans which enables these versatile molecules to be prepared in two steps from readily available aldehydes, alcohols and 3,3-diethoxypropyne. The reaction gives access to a wide range of 3-alkoxyfurans in good to excellent yield, and the products can be used in subsequent transformations to access more complex structures.

We would like to acknowledge the Engineering and Physical Sciences Research Council (EP/E052789/1 and EP/G040680/1) and GlaxoSmithKline (CASE award, PhD studentship support and supply of selected aldehydes) for supporting this work.

Notes and references

1 H. N. C. Wong, P. Yu and C.-Y. Yick, *Pure Appl. Chem.*, 1999, **71**, 1041.
2 (*a*) O. Gidron, Y. Diskin-Posner and M. Bendikov, *J. Am. Chem. Soc.*, 2010, **132**, 2148; (*b*) A. T. Yiu, P. M. Beaujuge, O. P. Lee, C. H. Woo, M. F. Toney and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 2012, **134**, 2180; (*c*) O. Gidron, A. Dadvand, Y. Sheynin, M. Bendikov and D. F. Perepichka, *Chem. Commun.*, 2011, **47**, 1976; (*d*) U. H. F. Bunz, *Angew. Chem., Int. Ed.*, 2010, **49**, 5037; (*e*) T. Fallon, A. C. Willis, A. D. Rae, M. N. Paddon-Row and M. S. Sherburn, *Chem. Sci.*, 2012, **3**, 2133.
3 (*a*) A. V. Gulevich, A. S. Dudnik, N. Chernyak and V. Gevorgyan, *Chem. Rev.*, 2013, **113**, 3084; (*b*) W. J. Moran and A. Rodríguez, *Org. Prep. Proced. Int.*, 2012, **44**, 103.
4 (*a*) M. Zheng, L. Huang, W. Wu and H. Jiang, *Org. Lett.*, 2013, **15**, 1838; (*b*) C. Song, L. Ju, M. Wang, P. Liu, Y. Zhang, J. Wang and Z. Xu, *Chem.–Eur. J.*, 2013, **19**, 3584.
5 (*a*) P. Lenden, D. A. Entwistle and M. C. Willis, *Angew. Chem., Int. Ed.*, 2011, **50**, 10657; (*b*) Y. Lian, T. Huber, K. D. Hesp, R. G. Bergman and J. A. Ellman, *Angew. Chem., Int. Ed.*, 2013, **52**, 629.
6 (*a*) B. Schmidt and D. Geißler, *Eur. J. Org. Chem.*, 2011, 7140; (*b*) B. Schmidt and D. Geißler, *Eur. J. Org. Chem.*, 2011, 4814; (*c*) K. Yamashita, Y. Yamamoto and H. Nishiyama, *J. Am. Chem. Soc.*, 2012, **134**, 7660.
7 C. He, S. Guo, J. Ke, J. Hao, H. Xu, H. Chen and A. Lei, *J. Am. Chem. Soc.*, 2012, **134**, 5766.
8 (*a*) X. Cui, X. Xu, L. Wojtas, M. M. Kim and X. P. Zhang, *J. Am. Chem. Soc.*, 2012, **134**, 19981; (*b*) H. Jiang, W. Zeng, Y. Li, W. Wu, L. Huang and W. Fu, *J. Org. Chem.*, 2012, **77**, 5179; (*c*) C. Wang, Z. Li, Y. Ju and S. Koo, *Eur. J. Org. Chem.*, 2011, 6976; (*d*) V. Rauniyar, Z. J. Wang, H. E. Burks and F. D. Toste, *J. Am. Chem. Soc.*, 2011, **133**, 8486; (*e*) H. Cao, H. Zhan, J. Wu, H. Zhong, Y. Lin and H. Zhang, *Eur. J. Org. Chem.*, 2012, 2138; (*f*) A. W. Sromek, A. V. Kel'in and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2004, **43**, 2280.
9 *Modern Gold Catalyzed Synthesis*, ed. A. S. K. Hashmi and F. D. Toste, Wiley-VCH, Weinheim, 2012.
10 (*a*) P. W. Davies, A. Cremonesi and L. Dumitrescu, *Angew. Chem., Int. Ed.*, 2011, **50**, 8931; (*b*) C. Gronnier, Y. Odabachian and F. Gagosz, *Chem. Commun.*, 2011, **47**, 218; (*c*) N. Krause and C. Winter, *Chem. Rev.*, 2011, **111**, 1994; (*d*) M. Ueda, A. Sato, Y. Ikeda, T. Miyoshi, T. Naito and O. Miyata, *Org. Lett.*, 2010, **12**, 2594; (*e*) S. Ngwerume and J. E. Camp, *Chem. Commun.*, 2011, **47**, 1857; (*f*) Z.-Y. Yan, Y. Xiao and L. Zhang, *Angew. Chem., Int. Ed.*, 2012, **51**, 8624.
11 (*a*) Y. Li, K. A. Wheeler and R. Dembinskia, *Adv. Synth. Catal.*, 2010, **352**, 2761; (*b*) H. Gao, X. Wu and J. Zhang, *Chem.–Eur. J.*, 2011, **17**, 2838; (*c*) X. Huang, B. Peng, M. Luparia, L. F. R. Gomes, L. F. Veiros and N. Maulide, *Angew. Chem., Int. Ed.*, 2012, **51**, 8886; (*d*) F. Liu, D. Qian, L. Li, X. Zhao and J. Zhang, *Angew. Chem., Int. Ed.*, 2010, **49**, 6669; (*e*) A. S. K. Hashmi, T. Häffner, M. Rudolph and F. Rominger, *Eur. J. Org. Chem.*, 2011, 667; (*f*) E. Li, W. Yao, X. Xie, C. Wang, Y. Shao and Y. Li, *Org. Biomol. Chem.*, 2012, **10**, 2960; (*g*) R. B. Dateer, K. Pati and R.-S. Liu, *Chem. Commun.*, 2012, **48**, 7200; (*h*) E. Wang, X. Fu, X. Xie, J. Chen, H. Gao and Y. Liu, *Tetrahedron Lett.*, 2011, **52**, 1968; (*i*) P. Nun, S. Dupuy, S. Gaillard, A. Poater, L. Cavallod and S. P. Nolan, *Catal. Sci. Technol.*, 2011, **1**, 58; (*j*) J. Li, L. Liu, D. Ding, J. Sun, Y. Ji and J. Dong, *Org. Lett.*, 2013, **15**, 2884.
12 (*a*) C. Meister and H. D. Scharf, *Synthesis*, 1981, 737; (*b*) A. Murai, K. Takahashi, H. Taketsuru and T. Masamune, *J. Chem. Soc., Chem. Commun.*, 1981, 221.
13 (*a*) J. D. Brubaker and A. G. Myers, *Org. Lett.*, 2007, **9**, 3523; (*b*) J. H. Frederich and P. G. Harran, *J. Am. Chem. Soc.*, 2013, **135**, 3788; (*c*) K.-I. Takao, H. Ochiai, K.-I. Yoshida, T. Hashizuka, H. Koshimura, K.-I. Tadano and S. Ogawa, *J. Org. Chem.*, 1995, **60**, 8179; (*d*) K. Okada, M. Mizuno, H. Sasaki, K. Sugiura, H. Tanino, H. Kakoi and S. Inoue, *Heterocycles*, 1991, **32**, 431.
14 T. J. Donohoe, A. A. Calabrese, J.-B. Guillermin, C. S. Frampton and D. Walter, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1748.
15 (*a*) S. Nakatani, M. Kirihara, K. Yamada and S. Tereshima, *Tetrahedron Lett.*, 1995, **36**, 8461; (*b*) P. Truong, X. Xu and M. P. Doyle, *Tetrahedron Lett.*, 2011, **52**, 2093; (*c*) A. F. Thomas and H. Damm, *Tetrahedron Lett.*, 1986, **27**, 505; see also ref. 12–13.
16 (*a*) M. N. Pennell, M. G. Unthank, P. Turner and T. D. Sheppard, *J. Org. Chem.*, 2011, **76**, 1479; (*b*) M. N. Pennell, P. G. Turner and T. D. Sheppard, *Chem.–Eur. J.*, 2012, **18**, 4748.
17 D. Obrecht, *Helv. Chim. Acta*, 1989, **72**, 447.
18 See ESI† for further details.
19 R. Kazlauskas, P. T. Murphy, R. J. Wells, J. J. Daly and P. Schönholzer, *Tetrahedron Lett.*, 1978, **19**, 4951.
20 (*a*) C. M. Krauter, A. S. K. Hashmi and M. Pernpointner, *ChemCatChem*, 2010, **2**, 1226; (*b*) P. Starkov, F. Rota, J. M. D'Oyley and T. D. Sheppard, *Adv. Synth. Catal.*, 2012, **354**, 3217; (*c*) A. S. K. Hashmi, L. Schwarz, P. Rubenbauer and M. C. Blanco, *Adv. Synth. Catal.*, 2006, **348**, 705; (*d*) A. S. K. Hashmi, *Catal. Today*, 2007, **122**, 211; (*e*) T. T. Dang, F. Boeck and L. Hintermann, *J. Org. Chem.*, 2011, **76**, 9353.
21 (*a*) A. S. K. Hashmi, in *Silver in Organic Chemistry*, ed. M. Harmata, John Wiley and Sons, Hoboken, 2010, pp. 357–359; (*b*) D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen and X. Shi, *J. Am. Chem. Soc.*, 2012, **134**, 9012.
22 R.-C. Gebel and P. Margaretha, *Helv. Chim. Acta*, 1992, **75**, 1633.
23 M.-A. Raheem, J. R. Nagireddy, R. Durham and W. Tam, *Synth. Commun.*, 2010, **40**, 2138.

ChemPubSoc Europe

DOI: 10.1002/chem.201406286

CHEMISTRY
A European Journal
Full Paper

Organic Synthesis

Irreversible *endo*-Selective Diels–Alder Reactions of Substituted Alkoxyfurans: A General Synthesis of *endo*-Cantharimides

Robert W. Foster,[a] Laure Benhamou,[a] Michael J. Porter,[a] Dejan-Krešimir Bučar,[a] Helen C. Hailes,[a] Christopher J. Tame,*[b] and Tom D. Sheppard*[a]

Abstract: The [4+2] cycloaddition of 3-alkoxyfurans with N-substituted maleimides provides the first general route for preparing *endo*-cantharimides. Unlike the corresponding reaction with 3*H* furans, the reaction can tolerate a broad range of 2-substitued furans including alkyl, aromatic, and heteroaromatic groups. The cycloaddition products were converted into a range of cantharimide products with promising lead-like properties for medicinal chemistry programs. Furthermore, the electron-rich furans are shown to react with a variety of alternative dienophiles to generate 7-oxabicyclo[2.2.1]heptane derivatives under mild conditions. DFT calculations have been performed to rationalize the activation effect of the 3-alkoxy group on a furan Diels–Alder reaction.

Introduction

To access new areas of chemical space, medicinal chemistry programs are increasingly focusing on fragments and scaffolds with rigid 3D structures that contain a significant proportion of sp^3 carbon atoms.[1] This in turn presents a considerable synthetic challenge as these molecules are generally not straightforward to synthesize, and late-stage derivatization is often far from trivial. Further challenges reside in the control of relative and absolute stereochemistry due to the presence of numerous chiral centres. Current structural scaffolds of interest include strained small-ring molecules (cyclopropanes, oxetanes, azetidines),[2] as well as fused (dihydrobenzofurans, indolines, tetrahydroquinolines)[3] and bridged bicylic and polycyclic compounds (bicyclopentanes, cubanes, etc).[4] Natural products have also traditionally provided chemists with inspiration, as they include bioactive molecules with complex 3D architectures.[5] Many of these compounds, however, have high molecular weights or are too structurally complex to be suitable for use as scaffolds for medicinal chemistry applications. Nevertheless, smaller natural products contain ring systems that are potentially ideal scaffolds for use in medicinal chemistry, provided that efficient synthetic routes can be developed with appropriate functional groups at positions on the central core.

The *exo*-cantharimide skeleton (Figure 1, derived from cantharidin, a natural product secreted by many species of blister beetle with well-established cytotoxic activity)[6] has been exploited in a wide range of molecules with useful biological properties. The motif is present in several cytotoxic compounds,[7] antiplasmodial agents,[8] androgen receptor antagonists[9] and in a positive allosteric modulator of the metabotropic glutamate receptor 4 (mGlu4).[10] More generally, the 7-oxabicyclo[2.2.1]heptyl skeleton is found in a number of other important natural products[11–13] and it has proved to be a valuable intermediate for synthetic chemists.[14–17] The properties of the *exo*-cantharimide skeleton have been extensively explored with a range of N-substituted derivatives showing useful biological properties. However, there are few methods for the introduction of substituents around the 7-oxabicyclo[2.2.1]heptyl ring system.[18] Furthermore, the corresponding *endo*-cantharimide scaffold has rarely been reported at all.[19]

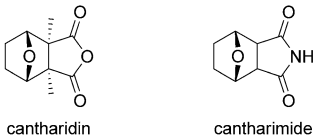


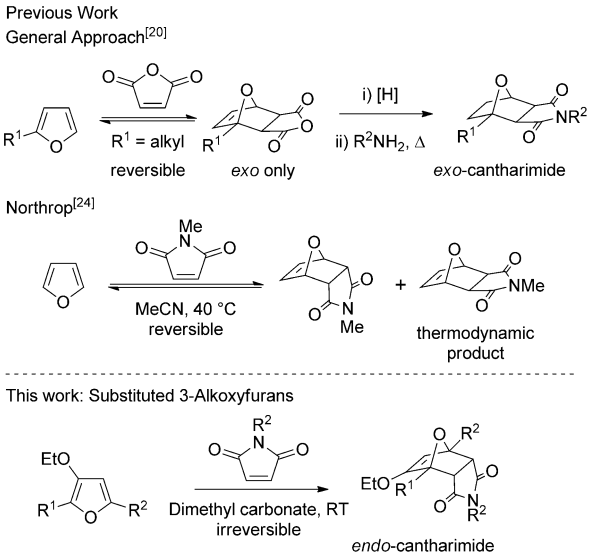
Figure 1. Natural product cantharidin and cantharimide.

The *exo*-cantharimide skeleton is typically prepared by the [4+2] cycloaddition of furans and maleic anhydride, followed by alkene reduction and condensation with an amine (Scheme 1).[20] A curious feature of the cycloaddition reaction is

[a] *R. W. Foster, Dr. L. Benhamou, Dr. M. J. Porter, Dr. D.-K. Bučar, Prof. H. C. Hailes, Dr. T. D. Sheppard*
Department of Chemistry, University College London
Christopher Ingold Laboratories, 20 Gordon Street
London, WC1H 0AJ (UK)
E-mail: tom.sheppard@ucl.ac.uk

[b] *Dr. C. J. Tame*
GlaxoSmithKline, Medicines Research Centre
Gunnels Wood Road, Stevenage, Herts, SG1 2NY (UK)
E-mail: christopher.j.tame@gsk.com

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201406286.

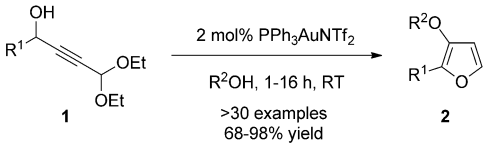


Scheme 1. Synthetic approaches to cantharimides.

the high stereoselectivity for the *exo* diastereomer observed, believed to be the result of a highly reversible cycloaddition process which is operating under thermodynamic control.[21,22] It is possible to access the corresponding *endo*-cantharimide by a Diels–Alder reaction of furan with maleimide;[23] however, experimental and computational studies have shown that this reaction is under thermodynamic control with the *exo*-cantharimide being the thermodynamic product.[24] As a consequence, the *endo*-adduct of maleimide and furan is known to rapidly isomerize either in hot solvent or when exposed to visible light, which impedes both the isolation and application of these compounds.[25] Another serious limitation of furan Diels–Alder reactions is that any deactivating substituents on the furan have a profound effect on the equilibrium position of the cyclization. For example, there are no reported examples of the [4+2] cycloaddition of 2-aryl or 2-heteroaryl furans with dienophiles of any type.

There is a long tradition of activating dienes for Diels–Alder reactions through the use of electron-donating substituents, which are known to reduce the activation energy for the cycloaddition reaction.[26] However, this is generally a kinetic effect and reducing the kinetic barriers to a thermodynamically controlled reaction would only increase the rate at which isomerization occurs. To access stable *endo*-cantharimides it is therefore necessary to develop reactions with a significantly improved thermodynamic driving force.[24]

We have recently developed a straightforward approach to 2-substituted-3-alkoxyfurans by gold-catalysed solvolytic cyclisation of suitably functionalised propargylic alcohols (Scheme 2).[27] Preliminary studies indicated that 3-alkoxyfurans underwent rapid and *endo*-selective reactions with *N*-methylmaleimide to generate kinetically stable cantharimide products. The distinct 3D structure of the *endo*-cantharimide motif, coupled with its physical properties, should make it a valuable new scaffold for medicinal chemistry applications. Such an approach should enable control of substituents at a variety of positions on the tricyclic ring system.



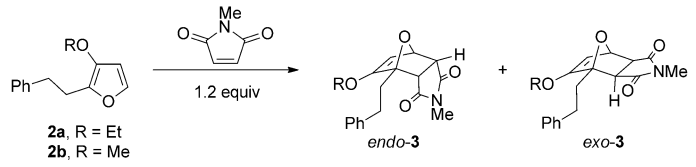
Scheme 2. Gold-catalysed synthesis of 3-alkoxyfurans **2** from propargylic alcohols **1**.[27]

Results and Discussion

The reaction of 3-ethoxyfuran **2a** with 1.2 equivalents of *N*-methylmaleimide proceed in a variety of solvents at room temperature to give cantharimide **3a** in near quantitative yield (Table 1, entries 1 to 4). Crucially the cantharimide was formed with a clear preference for the *endo* diastereomer and the two isomers could be readily separated by flash column chromatography. The identity of the solvent had little impact on yield or diastereoselectivity, so dimethyl carbonate (DMC) was selected on the grounds of its excellent environmental profile.[28] The reaction could also be scaled up to use 1 g of furan **2a**, giving cantharimide **3a** in 95% yield (entry 5, *endo*/*exo* ratio of 75:25). A purified sample of *endo*-**3a** was treated under the same reaction conditions and no isomerization was observed, suggesting the reaction proceeds under kinetic control. However, it was possible to increase the proportion of *exo*-**3a** by heating the reaction at 80 °C for 16 h (entry 6). The cyclization was equally effective when 3-methoxyfuran **2b** was used as a diene, giving the corresponding adduct in excellent yield as an 80:20 mixture of *endo* and *exo* diastereomers (entry 7).

These reaction conditions were applied to a wide range of 3-ethoxyfurans with different substituents at the 2-position,

Table 1. [4+2] cycloaddition of 3-alkoxyfurans **2** with *N*-methylmaleimide.



Entry	R	Solvent[a]	*T* [°C]	Reaction *t* [h]	Product	Yield [%]	*endo*/*exo*[b]
1	Et	Et_2O	25	4	**3a**	98[c]	65:35
2	Et	PhMe	25	4	**3a**	100[c]	65:35
3	Et	EtOH	25	4	**3a**	100[c]	70:30
4	Et	DMC	25	4	**3a**	93[d]	70:30
5[e]	Et	DMC	25	4	**3a**	95[d]	75:25
6	Et	DMC	80	16	**3a**	93[d]	55:45
7	Me	DMC	25	4	**3b**	89[d]	80:20

[a] DMC refers to dimethyl carbonate. [b] Determined by analysis of the crude ^{1}H NMR spectrum. [c] Yield determined by ^{1}H NMR spectroscopy using pentachlorobenzene as an internal standard. [d] Isolated yield. [e] Reaction conducted with 1.0 g of furan **2a**.

with the results summarized in Table 2. The reaction tolerated furans with primary and secondary aliphatic substituents (Table 2, entries 2 and 3). It was also possible to incorporate a *tert*-butoxycarbonyl (*N*-Boc) piperidine, as shown in entry 4. The reaction was very effective with an aromatic group at the 2-position, giving the first reported examples of 4-arylcantharimides (entries 5 to 10). The reaction of 2-phenylfuran **2 f** gave an 80:20 mixture of *endo* and *exo* diastereomers in good yield. This reaction could also be conducted on a 1.0 g scale, giving the two diastereomers **3 f** in a combined yield of 86%, and with complete isomeric separation following chromatography on silica gel. The relative stereochemistry of the two diastereomers was confirmed by X-ray crystallography (Figure 2).

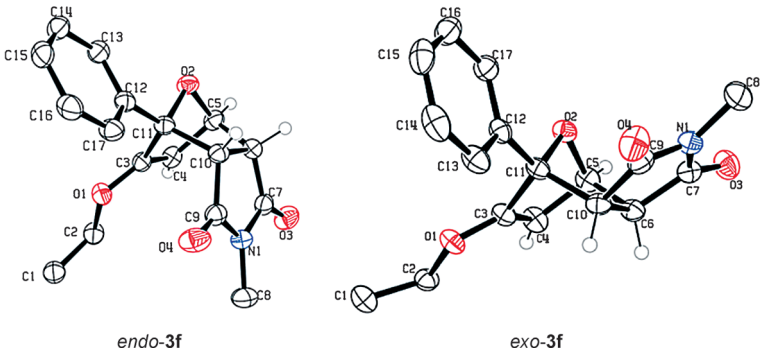
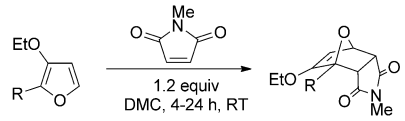


Figure 2. Crystal structures of cantharimides **3 f**. Ellipsoids are shown at the 50% probability level. Only hydrogen atoms belonging to the cyclic core are shown for clarity.[29]

Table 2. [4+2] cycloaddition of 3-alkoxyfurans **2** with *N*-methylmaleimide.

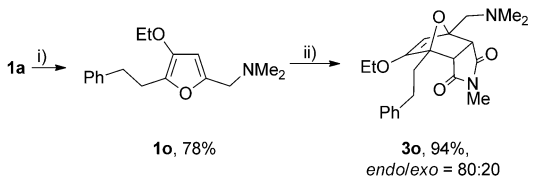


2 **3**

Entry	R		Isolated yield [%][a]	*endo*/*exo*[b]
1	Ph	**3a**	93	70:30
2		**3c**	95	85:15
3		**3d**	90	80:20
4	NBoc	**3e**	85	75:25
5		**3f**	86 (86)[c]	80:20
6	CF_3	**3g**	75	80:20
7	Br	**3h**	78	80:20
8	OMe	**3i**	95	80:20
9	CO_2Me	**3j**	84	75:25
10		**3k**	86	80:20
11	O	**3l**	85	90:10
12	S	**3m**	96	70:30
13	N	**3n**	92	70:30

[a] Combined isolated yield of *endo*-**3** and *exo*-**3**. [b] Determined by analysis of the ^{1}H NMR spectrum of the crude product. [c] Reaction conducted with 1.0 g of furan **2 f**.

The reaction was tolerant of electron-poor aromatic substituents (Table 2, entries 6 and 9), an electron-rich aromatic substituent (entry 8) and an aryl bromide substituent (entry 7). It was also possible to use a sterically encumbered 2-tolyl substituent to give cantharimide **3 k** in 86% yield. Furthermore, the reaction was effective when the 3-alkoxyfuran possessed a heteroaromatic substituent, as can be seen in entries 11 to 13 (85–96% yields). The chemoselective reaction of bis-furan **2 l** with *N*-methylmaleimide to give exclusively the enol ether adduct is an interesting demonstration of the high reactivity of the 3-alkoxyfuran unit in a [4+2] cycloaddition reaction. It was also possible to functionalize a 3-alkoxyfuran at the 5-position prior to the cycloaddition reaction, in order to introduce a substituent at the 7-position of the *endo*-cantharimide scaffold (Scheme 3).

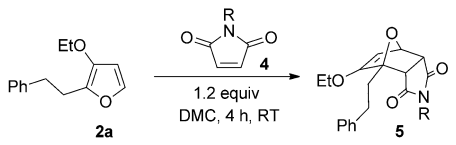


Scheme 3. Synthesis of a 7-substituted *endo*-cantharimide: i) ($H_2C{=}NMe_2$)I (2 equiv), MeCN, 16 h, RT; ii) *N*-methylmaleimide (1.2 equiv), DMC, 24 h, RT.

The cycloaddition of 3-alkoxyfuran **2 a** was effective with a number of alternative N-substituted maleimides, as illustrated in Table 3.[30] Sterically more challenging N-substituents could be incorporated in high yield and without an extended reaction time.

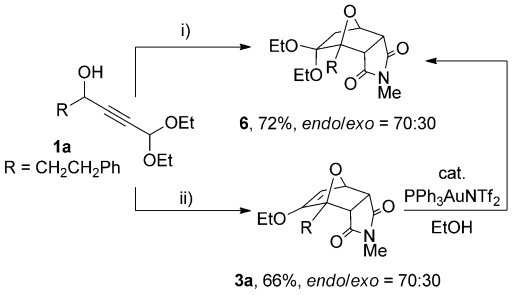
Additionally, it was possible to combine the gold-mediated furan synthesis with the cycloaddition reaction in a single step (Scheme 4, conditions i). Treating propargylic alcohol **1 a** with gold catalyst and *N*-methylmaleimide gave diethyl acetal **6** in good yield. It appeared that the gold catalyst was responsible for the in situ conversion of enol ether **3 a** into the corresponding diethyl acetal, as the interconversion can be avoided by poisoning the catalyst with 2.5 mol% PPh_3 prior to addition of

Table 3. [4+2] cycloaddition of 3-alkoxyfuran **2a** with maleimides **4**.



Entry	R	Yield **5** [%]	*endo*/*exo*[a]
1	Ph **4a**	94	65:35
2	4-MeC_6H_4 **4b**	83	55:35
3	c-Pr **4c**	87	60:40

[a] Determined by analysis of the ^{1}H NMR spectrum of the crude product.

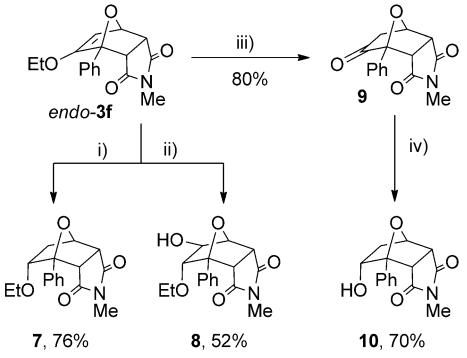


Scheme 4. One-pot cantharimide synthesis from propargylic alcohol **1a**. i) *N*-methylmaleimide, 2 mol% PPh_3AuNTf_2, EtOH; ii) 2 mol% PPh_3AuNTf_2, EtOH then 2.5 mol% PPh_3 then *N*-methylmaleimide.

the *N*-methylmaleimide, to give enol ether **3a** (*endo*/*exo* ratio of 70:30). Treatment of a sample of enol ether **3a** with catalytic PPh_3AuNTf_2 in ethanol was also observed to result in formation of acetal **6**.

Transformation of cycloaddition products

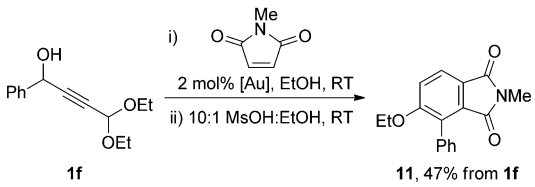
The *endo*-cantharimides contain an enol ether moiety, which can be readily transformed into a variety of functional groups (Scheme 5). For example, enol ether *endo*-**3f** can by hydrogenated to generate ether **7** with complete diastereocontrol.[31]



Scheme 5. Functional-group interconversion of enol ether *endo*-**3f**: i) H_2, 10% Pd/C; ii) 9-BBN then H_2O_2/NaOH; iii) SCX-2 cartridge; iv) $NaBH_4$, MeOH. 9-BBN = 9-borabicyclo[3.3.1]nonane.

The enol ether also underwent hydroboration and oxidation to give alcohol **8**, with complete regio- and stereocontrol. Enol ether *endo*-**3f** could be hydrolysed to give ketone **9** in good yield by passing it through a strong cation exchange (SCX-2) cartridge.[32] Treating ketone **9** with $NaBH_4$ afforded alcohol **10**, again with high stereocontrol.

The acid-mediated aromatization of 7-oxabicyclo[2.2.1]heptane derivatives has been previously applied to the synthesis of aromatic rings, and this approach could be used to prepare substituted phthalimide **11**.[33] The one-pot cantharimide synthesis described in Scheme 4 was used to convert alcohol **1f** into the crude cantharimide, which could be converted into phthalimide **11** by acid-mediated ring-opening and aromatization (Scheme 6).



Scheme 6. Synthesis of substituted phthalimide **11** by acid-catalysed aromatisation of cantharimide intermediates.

Physicochemical properties

An important challenge for drug development is the generation of novel heterocyclic building blocks with suitable properties for use in screening and medicinal chemistry programs.[34] The cantharimides accessed using this methodology have appropriate physicochemical properties for lead-like compounds, including lipophilicity,[35] molecular weight and polar surface area[36] (Figure 3). Another attractive feature of these scaffolds

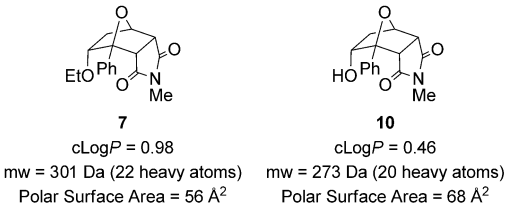
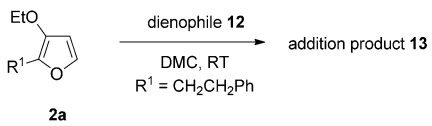


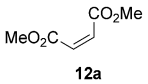
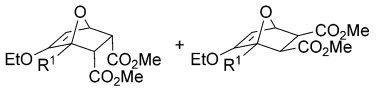
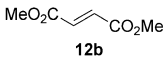
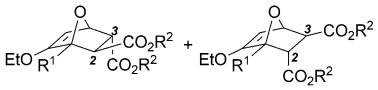
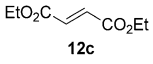
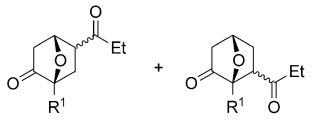
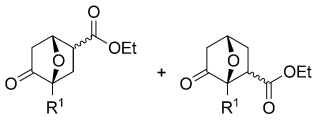
Figure 3. Physicochemical properties of *endo*-cantharimides.[39]

is the high proportion of sp^3-hybridized carbon atoms, which is typically associated with improved protein binding selectivity and frequency, better solubility and a reduced chance of off-target effects.[37] Indeed, cantharimides **7**, **10**, *endo*-**3f** and *exo*-**3f** were screened against the hERG receptor ($IC_{50} > 50$ μM) and the aryl hydrocarbon receptor ($EC_{50} > 100$ μM), which are responsible for common off target effects, and no affinity was observed. In addition the in vitro clearance of alcohol **10** in the presence of human microsomes was determined and only a low level of turnover was observed (< 0.53 mL min^{-1} g^{-1}).[38]

Table 4. [4+2] cycloaddition of 3-alkoxyfuran **2a** with different dienophiles.



2a

Entry	Dienophile **12**	Reaction *t* [h]	Product **13**	Isolated yield [%]	Product ratio[a]
1	 **12a**	72	 *endo*-**13a** + *exo*-**13a**	70	12:1
2	 **12b**	4		77	15:85
3	 **12c**	4	R^2 = Me, 3-*endo*-**13b**; R^2 = Et, 3-*endo*-**13c**; R^2 = Me, 3-*exo*-**13b**; R^2 = Et, 3-*exo*-**13c**	89	15:85
4[b,c]	 **12d**	16	 **13d** *endo/exo* = 60:40 + **13d'**	60	95:5
5[c,d]	 **12e**	6	 **13e** *endo/exo* = 70:30 + **13e'**	89	95: 5

[a] Determined by analysis of the ^{1}H NMR spectrum of the crude product. [b] Reaction conducted at 80 °C. [c] Crude product flushed through a SCX-2 cartridge. [d] Reaction conducted with 2 mol% $HfCl_4$.[41]

[4+2] cycloadditions with other dienophiles

The [4+2] cycloaddition of furans with maleate esters is known but was reported to require either forcing pressure[40] or high catalyst loadings of a Lewis acid.[41] In contrast, the catalyst-free reaction of dimethyl maleate **12a** and furan **2a** proceeded at room temperature to give adduct **13a** in a good yield and with excellent *endo* selectivity (Table 4, entry 1). The reactions of dimethyl and diethyl fumarate (**12b** and **12c**) with furan **2a** proceeded more rapidly, giving the corresponding adducts in 77–89% yield after 4 h (entries 2 and 3). There is a clear selectivity in both examples for the product which possessed *exo* stereochemistry with respect to the 3-position (3-*exo*-**13**).[42] Heating furan **2a** with ethyl vinyl ketone at 80 °C for 16 h, followed by hydrolysis of the enol ether on an SCX-2 cartridge, gave diketone **13d** with high regiocontrol (95:5), although as a 60:40 mixture of *endo*/*exo* isomers.

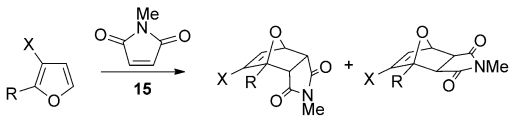
The catalyst-free reaction of furan **2a** with ethyl acrylate **12e** was relatively slow at room temperature, with <100% conversion after 24 h. However, it was possible to accelerate the reaction through the use of 2 mol% $HfCl_4$, giving the ketone **13e** in 89% yield and with good regiocontrol (95:5) after 6 h at room temperature (Table 4, entry 5). The catalyst loading for this reaction is much lower than the high (sometimes stoichiometric) loading reported for the Lewis acid-catalyzed reactions of 3*H* furans and acrylates.[41,43]

Computational study

The reactions of five 3-alkoxyfurans and *N*-methylmaleimide were explored with the M06-2X exchange–correlation function of Truhlar et al.,[44] a density functional that has been successfully used to model the reaction and activation energies of different cycloaddition processes.[45] 2-Substituted-3-methoxyfurans were chosen as suitable models for our 3-alkoxyfurans and these were compared to the corresponding 3*H* furans.

The 3-alkoxy group has a dramatic effect on the thermodynamics of the cycloaddition reaction, as is evident in Table 5. All five reactions of 3-alkoxyfurans have a clear thermodynamic driving force for the formation of both *endo*- and *exo*-addition products (Figure 5) and the data is consistent with a reaction that is likely to be kinetically controlled. In contrast, the values of ΔG for the corresponding reactions of 3*H* furans are all greater by 24–34 kJ mol^{-1}

Table 5. Calculated ΔG and $\Delta G^{\ddagger}$ for the reactions of furans **14** and *N*-methylmaleimide **15**.[a]



14 *endo*-**16** *exo*-**16**

14	R	X	*endo* ΔG	*endo* $\Delta G^{\ddagger}$	*exo* ΔG	*exo* $\Delta G^{\ddagger}$
14a	Me	OMe	−41.5	81.1	−47.7	82.1
14b	^{c}Pr	OMe	−44.1	75.0	−53.2	78.6
14c	4-MeOC_6H_4	OMe	−32.5	76.8	−30.1	85.3
14d	Ph	OMe	−34.0	83.6	−28.2	91.4
14e	4-$F_3CC_6H_4$	OMe	−25.3	85.9	−23.8	96.8
14f	Me	H	−11.8	97.9	−16.8	96.2
14g	^{c}Pr	H	−12.5	92.2	−10.3	92.8
14h	4-MeOC_6H_4	H	−6.1	95.4	−3.6	98.8
14i	Ph	H	−1.7	101.1	0.7	105.5
14j	4-$F_3CC_6H_4$	H	−0.9	101.6	0.9	108.3

[a] All values in kJ mol^{-1}. All data is calculated for species in the gas phase.

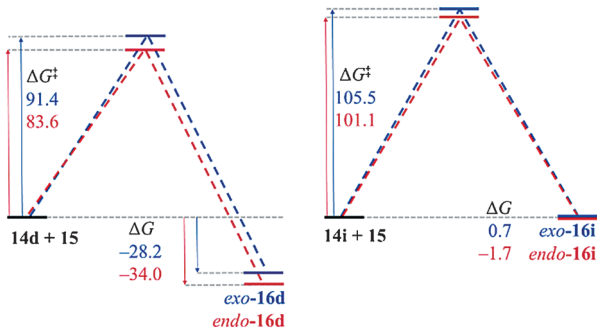


Figure 4. Calculated ΔG and $\Delta G^{\ddagger}$ values for the reactions of 2-phenylfurans **14d** and **14i** and *N*-methylmaleimide **15** in kJ mol^{-1}.

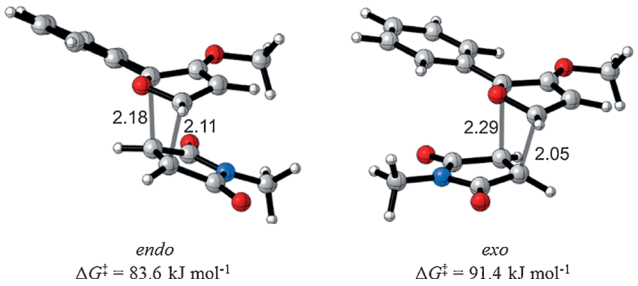
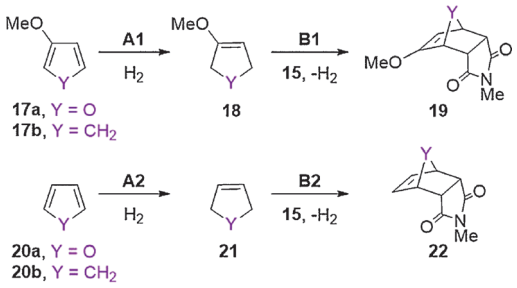


Figure 5. M06-2X/6-31G(d)-optimized *endo* and *exo* transition states for the reaction of furan **14d** and *N*-methylmaleimide **15**.[46] Distances in Å.

(Figure 4). This effect is most significant when the 2-substituent is aromatic, as this results in a value of ΔG close to zero for the furans **14h–j**. As expected, the 3-alkoxy group also has a significant effect on the free energy of activation for the cycloaddition reaction, with the kinetic barrier reduced by 11–23 kJ mol^{-1}. The effect of solvation on these reactions was also considered but was found to have little effect (see Supporting Information).

The reversibility of most furan Diels–Alder reactions has been attributed to the loss of aromatic stabilization upon formation of an adduct, which results in a facile retro-cycloaddition.[22] In order to examine the effect of a 3-methoxy group on this phenomenon, thermodynamic cycles involving the partial hydrogenation of 3-methoxyfuran **17a** and furan **20a** to the corresponding 2,5-dihydrofurans **18a** and **21a** were considered (Scheme 7). It is notable that the free energy of hydrogenation for furan **20a** was 25.9 kJ mol^{-1} greater than for 3-methoxyfuran **17a**. The corresponding reaction free energies for cyclopentadienes **17b** and **20b** were also calculated but no significant difference was observed. The implications of these calculations are that 1) the difference in behaviour between 3*H* and 3-methoxy furans in cycloaddition reactions can be attributed to differences associated with loss of aromaticity rather than with C–C bond formation and 2) a 3-methoxy group can reduce the energetic penalty associated with the loss of aromaticity upon the Diels–Alder reaction of a furan, increasing the thermodynamic stability of the cycloaddition product.



Y = O; ΔG (A1) – ΔG (A2) = –25.9 kJ mol^{-1}
ΔG (B1) – ΔG (B2) = –2.3 kJ mol^{-1}
Y = CH_2; ΔG (A1) – ΔG (A2) = –0.1 kJ mol^{-1}
ΔG (B1) – ΔG (B2) = –3.5 kJ mol^{-1}

Scheme 7. Thermodynamic cycle involving the hydrogenation of dienes **17** and **20**.

Conclusions

We have demonstrated that 3-alkoxyfurans are excellent dienes for [4+2] cycloadditions with a wide variety of maleimides and other dienophiles. This methodology significantly expands the nature of cantharimides that can be readily prepared with high *endo* selectivity. The reaction tolerates alkyl, aryl and heteroaryl substituents and the enol ether cycloaddition product can be transformed into a diverse collection of drug-like compounds. Finally, DFT calculations have confirmed that a 3-alkoxy group has a significant effect on both the thermodynamic driving-force and the activation energy of the Diels–Alder reaction of 2-substituted furans with *N*-methylmaleimides. The former effect can potentially be attributed to the 3-alkoxygroup leading to a reduced energetic penalty associated with the loss of furan aromaticity that occurs during the cycloaddition reaction.

Experimental Section

General cycloaddition procedure

A solution of the maleimide (1.2 equiv) in dimethyl carbonate (3.6 M) was added to a stirring solution of 3-alkoxyfuran (1.0 equiv) in dimethyl carbonate (1.5 M) at room temperature and the reaction stirred at room temperature for 4–24 h. The reaction was then diluted with ethyl acetate and loaded onto an aminopropyl cartridge. After 5 min the cartridge was then flushed with ethyl acetate and the solvent removed in vacuo to give the crude cycloaddition product.

Experimental procedures, ^{1}H and ^{13}C NMR spectra, characterization data of all compounds, compound screening data, details of computational studies including energy minimized geometries and XRD crystallography files are available in the Supporting Information.

Acknowledgements

This work was supported by GlaxoSmithKline and the Engineering and Physical Sciences Research Council (EPSRC Industrial CASE Award) and the UCL Ph.D. program in Drug Discovery.

Keywords: cantharimides · cycloadditions · dienes · furans · phthalimide

[1] a) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752 – 6756; b) J. L. Reymond, R. van Deursen, L. C. Blum, L. Ruddigkeit, *Med. Chem. Commun.* **2010**, *1*, 30 – 38; c) L. C. Blum, J. L. Reymond, *J. Am. Chem. Soc.* **2009**, *131*, 8732 – 8733; d) T. J. Ritchie, S. J. F. MacDonald, *Drug Discovery Today* **2009**, *14*, 1011 – 1020.

[2] Cyclopropanes: a) F. Gnad, O. Reiser, *Chem. Rev.* **2003**, *103*, 1603 – 1624; b) S. Ishikawa, T. D. Sheppard, J. M. D'Oyley, A. Kamimura, W. B. Motherwell, *Angew. Chem. Int. Ed.* **2013**, *52*, 10060 – 10063; *Angew. Chem.* **2013**, *125*, 10244 – 10247. Oxetanes: c) J. A. Burkhard, G. Wuitschik, M. Rogers-Evans, K. Müller, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 9052 – 9067; *Angew. Chem.* **2010**, *122*, 9236 – 9251; d) O. A. Davis, J. A. Bull, *Angew. Chem. Int. Ed.* **2014**, *53*, 14230 – 14234; *Angew. Chem.* **2014**, *126*, 14454 – 14458. Azetidines: e) G. Wuitschik, M. Rogers-Evans, A. Buckl, M. Bernasconi, M. Märki, T. Godel, H. Fischer, B. Wagner, I. Parrilla, F. Schuler, J. Schneider, A. Alker, W. B. Schweizer, K. Müller, E. M. Carreira, *Angew. Chem. Int. Ed.* **2008**, *47*, 4512 – 4515; *Angew. Chem.* **2008**, *120*, 4588 – 4591.

[3] a) D. Liu, G. Zhao, L. Xiang, *Eur. J. Org. Chem.* **2010**, 3975 – 3984; b) F. Bertolini, M. Pineschi, *Org. Prep. Proced. Int.* **2009**, *41*, 385 – 418.

[4] a) A. F. Stepan, C. Subramanyam, I. V. Efremov, J. K. Dutra, T. J. O'Sullivan, K. J. DiRico, W. S. McDonald, A. Won, P. H. Dorff, C. E. Nolan, S. L. Becker, L. R. Pustilnik, D. R. Riddell, G. W. Kauffman, B. L. Kormos, L. Zhang, Y. Lu, S. H. Capetta, M. E. Green, K. Karki, E. Sibley, K. P. Atchison, A. J. Hallgren, C. E. Oborski, A. E. Robshaw, B. Sneed, C. J. O'Donnell, *J. Med. Chem.* **2012**, *55*, 3414 – 3424; b) J. Wlochal, R. D. M. Davies, J. Burton, *Org. Lett.* **2014**, *16*, 4094 – 4097.

[5] D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2007**, *70*, 461 – 477.

[6] a) A. McCluskey, M. C. Bowyer, E. Collins, A. T. R. Sim, J. A. Sakoff, M. L. Baldwin, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1687 – 1690; b) A. McCluskey, S. P. Ackland, M. C. Bowyer, M. L. Baldwin, J. Garner, C. C. Walkom, J. A. Sakoff, *Bioorg. Chem.* **2003**, *31*, 68 – 79.

[7] a) S. H. L. Kok, C. H. Chui, W. S. Lam, J. Chen, F. Y. Lau, R. S. M. Wong, G. Y. M. Cheng, P. B. S. Lai, T. W. T. Leung, M. W. Y. Yu, J. C. O. Tanga, A. S. C. Chan, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1155 – 1159; b) L. H. Lin, H.-S. Huang, C. C. Lin, L.-W. Lee, P. Y. Lin, *Chem. Pharm. Bull.* **2004**, *52*, 855 – 857; c) R. M. Attar, M. Jure-Kunkel, A. Balog, M. E. Cvijic, J. Dell-John, C. A. Rizzo, L. Schweizer, T. E. Spires, J. S. Platero, M. Obermeier, W. Shan, M. E. Salvati, W. R. Foster, J. Dinchuk, S. J. Chen, G. Vite, R. Kramer, M. M. Gottardis, *Cancer Res.* **2009**, *69*, 6522 – 6530; d) T. Shimizu, M. Iizuka, H. Matsukura, D. Hashizume, M. Sodeoka, *Chem. Asian J.* **2012**, *7*, 1221 – 1230; e) A. McCluskey, C. Walkom, M. C. Bowyer, S. P. Ackland, E. Gardiner, J. A. Sakoff, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2941 – 2946; f) B. E. Campbell, M. Tarleton, C. P. Gordon, J. A. Sakoff, J. Gilbert, A. McCluskey, R. B. Gasser, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3277 – 3281.

[8] J. Bajsa, A. McCluskey, C. P. Gordon, S. G. Stewart, T. A. Hill, R. Sahu, S. O. Duke, B. L. Tekwani, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6688 – 6695.

[9] M. E. Salvati, A. Balog, W. Shan, R. Rampulla, S. Giese, T. Mitt, J. A. Furch, G. D. Vite, R. M. Attar, M. Jure-Kunkel, J. Geng, C. A. Rizzo, M. M. Gottardis, S. R. Krystek, J. Gougoutas, M. A. Galella, M. Obermeier, A. Furad, G. Chandrasena, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1910 – 1915.

[10] C. K. Jones, D. W. Engers, A. D. Thompson, J. R. Field, A. L. Blobaum, S. R. Lindsley, Y. Zhou, R. D. Gogliotti, S. Jadhav, R. Zamorano, J. Bogenpohl, Y. Smith, R. Morrison, J. S. Daniels, C. D. Weaver, P. J. Conn, C. W. Lindsley, C. M. Niswender, C. R. Hopkins, *J. Med. Chem.* **2011**, *54*, 7639 – 7647.

[11] a) M. Tori, T. Torii, K. Tachibana, S. Yamada, T. Tsuyuki, T. Takahashi, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 469 – 472; b) Y. Yamano, M. Ito, A. Wada, *Org. Biomol. Chem.* **2008**, *6*, 3421 – 3427; c) C. L. Lee, L. C. Chiang, L. H. Cheng, C. C. Liaw, M. H. A. El-Razek, F. R. Chang, Y. C. Wu, *J. Nat. Prod.* **2009**, *72*, 1568 – 1572; d) A. Kusano, M. Shibano, G. Kussano, T. Miyase, *Chem. Pharm. Bull.* **1996**, *44*, 2078 – 2085.

[12] a) E. N. Pitsinos, N. Athinaios, V. P. Vidali, *Org. Lett.* **2012**, *14*, 4666 – 4669; b) A. Yajima, F. Saitou, M. Sekimoto, S. Maetoko, T. Nukada, G. Yabuta, *Tetrahedron* **2005**, *61*, 9164 – 9172.

[13] Y. T. Lin, F. Y. Lin, M. Isobe, *Org. Lett.* **2014**, *16*, 5948 – 5951.

[14] a) P. Vogel, D. Fattori, F. Gasparini, C. Le Drian, *Synlett* **1990**, 173 – 185; b) T. Hudlicky, D. A. Entwistle, K. K. Pitzer, A. J. Thorpe, *Chem. Rev.* **1996**, *96*, 1195 – 1220.

[15] P. A. Grieco, R. E. Zelle, R. Lis, J. Finn, *J. Am. Chem. Soc.* **1983**, *105*, 1403 – 1404.

[16] J. Y. Sim, G. S. Hwang, K. H. Kim, E. M. Ko, D. H. Ryu, *Chem. Commun.* **2007**, 5064 – 5065.

[17] a) M. Shoji, Y. Hayashi, *Eur. J. Org. Chem.* **2007**, 3783 – 3800; b) M. Shoji, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1672 – 1690.

[18] a) G. Göksu, M. Gül, N. Öcal, D. E. Kaufmann, *Tetrahedron Lett.* **2008**, *49*, 2685 – 2688; b) L. P. Deng, F. M. Liu, H. Y. Wang, *J. Heterocycl. Chem.* **2005**, *42*, 13 – 18.

[19] a) S. Jarosz, M. Mach, K. Szewczyk, S. Skóra, Z. Ciunik, *Eur. J. Org. Chem.* **2001**, 2955 – 2964; b) S. J. Howell, N. Spencer, D. Philp, *Org. Lett.* **2002**, *4*, 273 – 276.

[20] G. H. Grogan, L. M. Rice, *J. Med. Chem.* **1963**, *6*, 802 – 805.

[21] D. Tobia, R. Harrison, B. Phillips, T. L. White, M. DiMare, B. Rickborn, *J. Org. Chem.* **1993**, *58*, 6701 – 6706.

[22] L. Rulísek, P, Šebek, Z. Havlas, R. Hrabal, P. Čapek, A. Svatos, *J. Org. Chem.* **2005**, *70*, 6295 – 6302.

[23] Y. W. Goh, B. R. Pool, J. M. White, *J. Org. Chem.* **2008**, *73*, 151 – 156.

[24] R. C. Boutelle, B. H. Northrop, *J. Org. Chem.* **2011**, *76*, 7994 – 8002.

[25] H. Kwart, I. Burchuk, *J. Am. Chem. Soc.* **1952**, *74*, 3094 – 3097.

[26] a) S. Danishefsky, T. Kitahara, *J. Am. Chem. Soc.* **1974**, *96*, 7807 – 7808; b) S. A. Kozmin, V. H. Rawal, *J. Org. Chem.* **1997**, *62*, 5252 – 5253; c) J. M. Holmes, A. L. Albert, M. Gravel, *J. Org. Chem.* **2009**, *74*, 6406 – 6409; d) S. Zhou, E. Sánchez-Larios, M. Gravel, *J. Org. Chem.* **2012**, *77*, 3576 – 3582; e) J. Choi, H. Park, H. J. Yoo, S. Kim, E. J. Sorensen, C. Lee, *J. Am. Chem. Soc.* **2014**, *136*, 9918 – 9921.

[27] M. N. Pennell, R. W. Foster, P. G. Turner, H. C. Hailes, C. J. Tame, T. D. Sheppard, *Chem. Commun.* **2014**, *50*, 1302 – 1304.

[28] a) R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, A. D. Curzons, *Green Chem.* **2011**, *13*, 854 – 862; b) T. Laird, *Org. Process Res. Dev.* **2012**, *16*, 1 – 2.

[29] CCDC 1035038 and 1035039 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[30] S. P. Borikar, V. Paul, V. G. Puranik, V. T. Sathe, S. Lagunas-Rivera, M. Ordónez, *Synthesis* **2011**, *10*, 1595 – 1598.

[31] H. Wang, K. Houk, *Chem. Sci.* **2014**, *5*, 462 – 470.

[32] Biotage ISOLUTE SCX-2 solid phase extraction column.

[33] a) R. N. Ram, N. Kumar, *Tetrahedron* **2008**, *64*, 10267 – 10271; b) R. Medimagh, S. Marque, D. Prim, J. Marrot, S. Chatti, *Org. Lett.* **2009**, *11*, 1817 – 1820; c) M. Romero, P. Renard, D. H. Caignard, G. Atassi, X. Solans, P. Constans, C. Bailly, M. D. Pujol, *J. Med. Chem.* **2007**, *50*, 294 – 307; d) M. Ball, A. Boyd, G. Churchill, M. Cuthbert, M. Drew, M. Fielding, G. Ford, L. Frodsham, M. Golden, K. Leslie, S. Lyons, B. McKeever-Abbas, A. Stark, P. Tomlin, *Org. Process Res. Dev.* **2012**, *16*, 741 – 747; e) A. Peter, B. Singaram, *Tetrahedron Lett.* **1982**, *23*, 245 – 258; f) P. S. Sarang, A. A. Yadav, P. S. Patil, U. M. Krishna, G. K. Trivedi, M. M. Salunkhe, *Synthesis* **2007**, 1091 – 1095; g) E. Mahmoud, D. A. Watson, R. F. Lobo, *Green Chem.* **2014**, *16*, 167 – 175.

[34] a) S. J. Teague, A. M. Davis, P. D. Leeson, T. Oprea, *Angew. Chem. Int. Ed.* **1999**, *38*, 3743 – 3748; *Angew. Chem.* **1999**, *111*, 3962 – 3967; b) A. Nadin, C. Hattotuwagama, I. Churcher, *Angew. Chem. Int. Ed.* **2012**, *51*, 1114 – 1122; *Angew. Chem.* **2012**, *124*, 1140 – 1149.

[35] a) P. D. Leeson, B. Springthorpe, *Nat. Rev. Drug Discovery* **2007**, *6*, 881 – 890; b) P. Gleeson, G. Bravi, S. Modi, D. Lowe, *Bioorg. Med. Chem.* **2009**, *17*, 5906 – 5919; c) J. D. Hughes, J. Blagg, D. A. Price, S. Bailey, G. A. DeCrescenzo, R. V. Devraj, E. Ellsworth, Y. M. Fobian, M. E. Gibbs, R. W. Gilles, N. Greene, E. Huang, T. Krieger-Burke, J. Loesel, T. Wager, L. Whiteley, Y. Zhang, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4872 – 4875.

[36] J. Linnankoski, J. M. Mäkelä, V. P. Ranta, A. Urtti, M. Yliperttula, *J. Med. Chem.* **2006**, *49*, 3674 – 3681.

[37] P. A. Clemons, N. E. Bodycombe, H. A. Carrinski, J. A. Wilson, A. F. Shamji, B. K. Wagner, A. N. Koehler, S. L. Schreiber, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 18787 – 18792.

[38] IVC testing performed by Cyprotex, 15 Beech Lane, Macclesfield, Cheshire, SK10 2DR, UK.

[39] Polar Surface Area and.clog P were calculated using ChemBioDraw Ultra 14.0, CambridgeSoft.
[40] a) H. Kotsuki, H. Nishizawa, M. Ochi, K. Matsuoka, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 496 – 499; b) A. McCluskey, M. A. Keane, C. C. Walkom, M. C. Bowyer, A. T. R. Sim, D. J. Young, J. A. Sakoff, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 391 – 393.
[41] Y. Hayashi, M. Nakamura, S. Nakao, T. Inoue, M. Shoji, *Angew. Chem. Int. Ed.* **2002**, *41*, 4079 – 4082; *Angew. Chem.* **2002**, *114*, 4253 – 4256.
[42] A. J. Kassick, J. Jiang, J. Bunda, D. Wilson, J. Bao, H. Lu, P. Lin, R. G. Ball, G. A. Doss, X. Tong, K. L. C. Tsao, H. Wang, G. Chicchi, B. Karanam, R. Tschirret-Guth, K. Samuel, D. F. Hora, S. Kumar, M. Madeira, W. Eng, R. Hargreaves, M. Purcell, L. Gantert, J. Cook, R. J. DeVita, S. G. Mills, *J. Med. Chem.* **2013**, *56*, 5940 – 5948.
[43] a) H. Kotsuki, K. Asao, H. Ohnishi, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3339 – 3340; b) J. A. Moore, E. M. Partain, *J. Org. Chem.* **1983**, *48*, 1105 – 1106; c) F. Brion, *Tetrahedron Lett.* **1982**, *23*, 5299 – 5302.
[44] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215 – 241.
[45] R. S. Paton, S. Kim, A. G. Ross, S. J. Danishefsky, K. N. Houk, *Angew. Chem. Int. Ed.* **2011**, *50*, 10366 – 10368; *Angew. Chem.* **2011**, *123*, 10550 – 10552.
[46] CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, **2009** (http://www.cylview.org).

Received: November 29, 2014
Published online on March 10, 2015

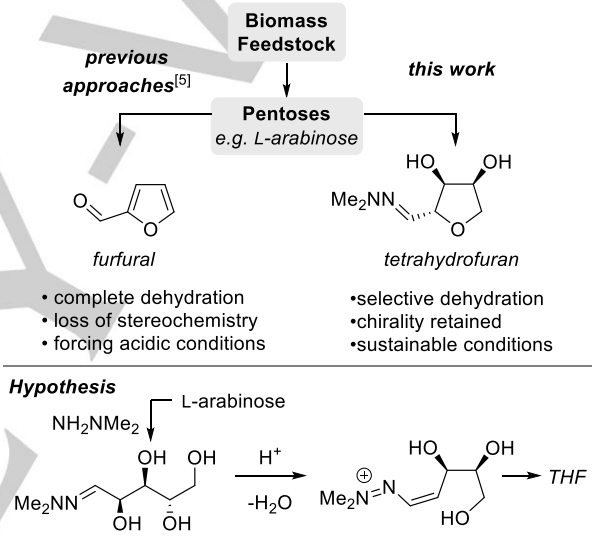
COMMUNICATION

Sustainable Synthesis of Chiral Tetrahydrofurans *via* the Selective Dehydration of Pentoses

Robert W. Foster,[a] Christopher J. Tame,[b] Dejan-Krešimir Bučar,[a] Helen C. Hailes,[a] and Tom D. Sheppard[a]

Abstract: *L-Arabinose is an abundant resource available as a waste product of the sugar beet industry. Through use of a hydrazone-based umpolung strategy, L-arabinose was selectively dehydrated to form a chiral tetrahydrofuran on a multi-gram scale without the need for protecting groups. This approach was extended to other biomass-derived reducing sugars and the mechanism of the key cyclization investigated. This methodology was applied to the synthesis of chiral tetrahydrofurans, including a formal synthesis of 3R-3-hydroxymuscarine.*

The more effective use of biomass, and in particular that generated as waste,[1] is essential to reduce the global dependence on petrochemical resources for the manufacture of valuable compounds, fuels and materials.[2] The majority of biomass is made up of carbohydrates, which are an abundant source of pentoses and hexoses.[3] For example, the refinement of sugar beet generates beet pulp as a major waste product, and this is a rich source of L-arabinose.[4] A variety of techniques have been developed to convert these biomass resources into valuable small molecules, such as the dehydration of pentoses under forcing acidic conditions to give furfural (Scheme 1), which can then be converted into various alcohols, alkenes and heterocycles.[5] However, the majority of compounds prepared from pentoses and hexoses in this fashion are either achiral[6] or racemic mixtures where the stereochemistry of the chiral precursors is lost.[7] Therefore using these products as intermediates in the synthesis of more complex targets may require the reintroduction or single-isomeric stereocentres using asymmetric catalysis[8] or resolutions.[9]
The tetrahydrofuran (THF) is a privileged scaffold within medicinal chemistry[10] and the stereoselective synthesis of chiral THFs has been an major area of recent research.[11] An attractive approach is to utilize the inherent chirality present in single isomer biomass-derived carbohydrates.[12] However, existing methods often require the selective conversion of a primary alcohol into an alkyl sulfonate or halide [13] and/or the use of protecting groups,[14] both of which are detrimental to the economy of a synthetic route.[15] Herein we describe the application of *N,N*-dimethylhydrazine[16] for the selective dehydration of biomass-derived reducing sugars to prepare chiral THFs under mildly acidic conditions (Scheme 1).[17]



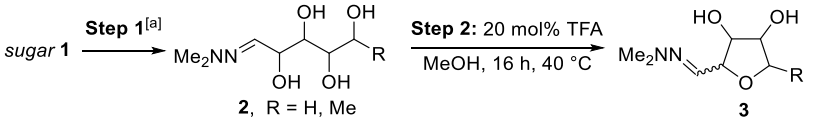
Scheme 1. The preparation of furfural and THFs from biomass feedstock.

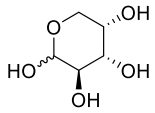
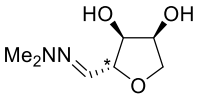
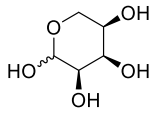
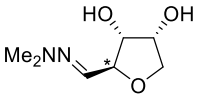
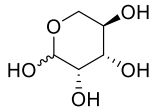
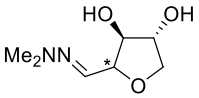
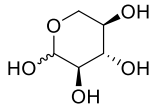
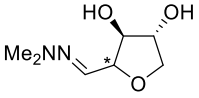
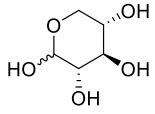
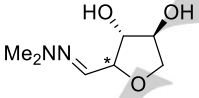
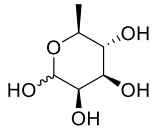
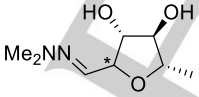
Treating L-arabinose **1a** with *N,N*-dimethylhydrazine and Amberlyst® 15 acidic resin in methanol at room temperature gave hydrazone **2a** in 99% yield (Table 1). Stirring hydrazone **2a** in methanol at 40 °C for 16 h with 20 mol% TFA resulted in 100% conversion of **2a**. Analysis of the crude ^{1}H NMR indicated the formation of THF **3a** as a 75:25 mixture of diastereoisomers and purification by flash column chromatography gave a mixture of the two stereoisomers in 67% yield. The reaction was scaled up from a 6.7 mmol scale to a 104 mmol scale without any significant drop in yield, giving 11.9 g of THF **3a**. The major diastereoisomer was isolated by recrystallization and the stereochemistry was confirmed by single crystal X-ray diffraction (Figure 1). Both steps were conducted in a sustainable solvent[18] (methanol) without the need for either pre-drying or for a drying agent to be present.
The same reaction conditions were used to prepare the enantiomeric THF *ent*-**3a** from D-ribose (Table 1, entry 2) in a 59% yield over two steps. It is notable that the diastereoselectivity of this reaction was comparable with that observed for the cyclization of arabinose-derived hydrazone **2a**.

[a] Mr. R. W. Foster, Professor H. C. Hailes, Dr. T. D. Sheppard
Department of Chemistry, University College London
Christopher Ingold Laboratories
20 Gordon Street, London, WC1H 0AJ, (UK)
E-mail: tom.sheppard@chem.ucl.ac.uk.
[b] Dr. C. J. Tame
GlaxoSmithKline
Medicines Research Centre
Gunnels Wood Road, Stevenage, Herts, SG1 2NY, (UK)

Supporting information for this article is given via a link at the end of the document.

Table 1. Two-step synthesis of THFs **3** from sugars **1**.



Entry	Sugar **1**	**Step 1** yield/%	THF **3**[b]	**Step 2** yield%	*d.r.*[c]
1	 L-arabinose **1a**	99	 **3a**	67 (66)[d]	75:25
2	 D-ribose **1b**	98	 *ent*-**3a**	59	75:25
3	 D-lyxose **1c**	98	 **3b**	66	55:45
4	 D-xylose **1d**	not isolated	 **3b**	61[e]	55:45
5	 L-xylose *ent*-**1d**	not isolated	 *ent*-**3b**	57[e]	55:45
6	 L-rhamnose **1e**	99	 **3c**	69	60:40

[a] Reagents and Conditions: NH_2NMe_2 (2 equiv.), Amberlyst® 15, MeOH, 24 h, RT. [b] Reaction conducted on a 6.00–6.70 mmol scale unless otherwise stated. [c] Determined by analysis of the crude ^1H NMR spectra. [d] Reaction conducted using 20.0 g (104 mmol) of hydrazone **2a**. [e] Yield over two steps from xylose.

The methodology was also extended to D-lyxose (Table 1, entry 3), with the corresponding hydrazone prepared in good yield. The TFA-mediated cyclization step gave THF **3b** in 66% yield as a 55:45 mixture of diastereoisomers. THF **3b** could also be prepared from D-xylose in 61% yield over two steps, again as a 55:45 mixture of diastereoisomers (entry 4). This is a particularly important result as D-xylose is one of the major components of biomass.[3] Xylose is naturally available in both enantiomers and using L-xylose it was possible to access *ent*-**3b** in a comparable yield (entry 5). The methodology was extended to deoxy sugar L-Rhamnose, another constituent of sugar beet pulp, to give THF **3c** in 69% yield as a 60:40 mixture of diastereoisomers (entry 6).

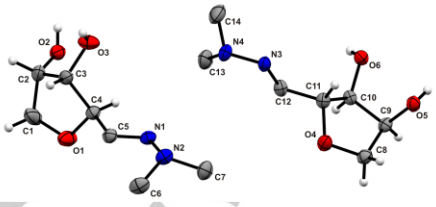
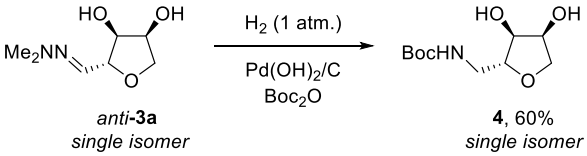


Figure 1. ORTEP of the asymmetric unit in the crystal structure of hydrazone *anti*-**3a.** The thermal ellipsoids are shown at a 50% probability level. Only hydrogen atoms belonging to the cyclic core are shown for clarity.[19]

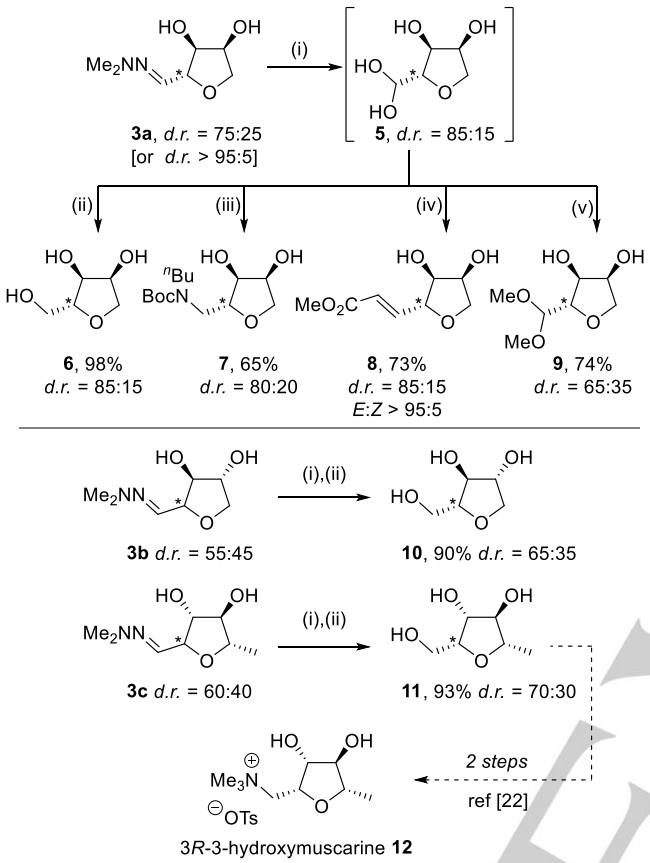
Recrystallization of hydrazone **3a** yielded the major *anti*-diastereoisomer in high purity. Reducing hydrazone *anti*-**3a** using hydrogen, a palladium catalyst and Boc_2O gave carbamate **4** in 60% yield as a single stereoisomer (Scheme 2).

Treatment of THF **3a** (*d.r.* = 75:25) with Amberlyst® 15 acidic resin in water at room temperature resulted in rapid hydrolysis of the hydrazone to give hydrolyzed product **5** (Scheme 3).[20] Reduction of compound **5** with $NaBH_4$ in methanol gave triol **6** as an 85:15 mixture of diastereoisomers in 98% yield over two steps from hydrazone **3a.** Reductive amination of intermediate **5** using *n*-butylamine, acetic acid and hydrogen/palladium, followed by trapping of the intermediate amine with Boc_2O, gave carbamate **7** in 65% yield from hydrazone **3a** as an 80:20 mixture of diastereoisomers. Compound **5** was also converted to alkene **8** using trimethyl phosphonoacetate in 73% yield over two steps with excellent *E*-selectivity. Finally, treating compound **6** with Amberlyst® 15 in methanol resulted in the formation of dimethyl acetal **9** in 74% yield over two steps from **3a** as a 65:35 mixture of stereoisomers. The hydrolysis/reduction sequence was also applied to the hydrazones **3b** and **3c**, gave the corresponding triols **10** and **11** in 90% and 93% yield respectively. L-Rhamnose-derived triol **11** is a late-stage intermediate in Fleet's synthesis of



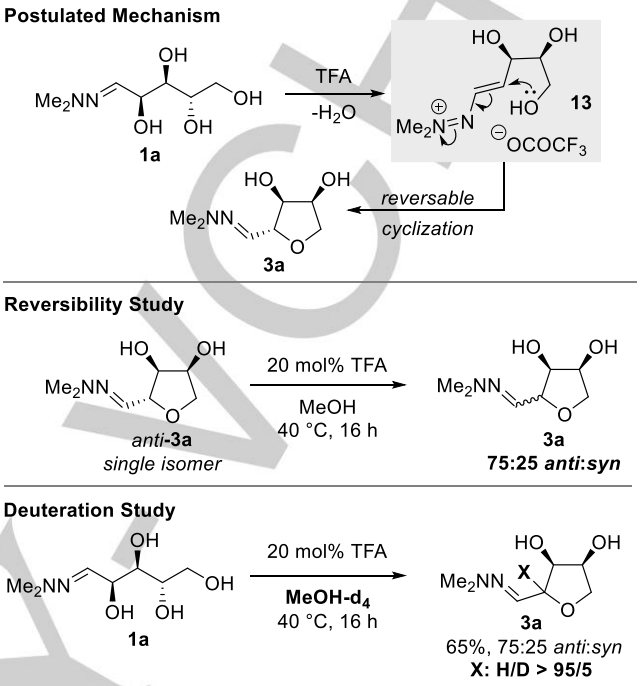
Scheme 2. Reduction of hydrazone *anti*-**3a.** Reagents and conditions; H_2 (1 atm.), $Pd(OH)_2/C$, Boc_2O, CPME, 24 h, RT.

3*R*-3-hydroxymuscarine **12**.[21] Triol **11** was previously prepared from L-rhamnose using stoichiometric bromine, trifluoromethanesulfonic anhydride and lithium aluminium hydride, so our route represents a less hazardous and more sustainable alternative.



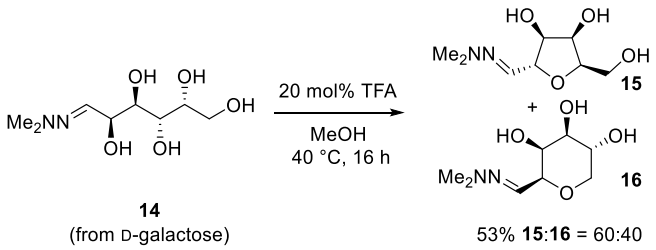
Scheme 4. Hydrolysis of hydrazones **3** and transformation into a range of tetrahydrofuran products. Reagents and conditions; (i) Amberlyst® 15, H_2O, 5 minutes, RT; (ii) $NaBH_4$, MeOH, 1 h, 0 °C; (iii) *n*-$BuNH_2$, AcOH, H_2 (1 atmosphere), 10% Pd/C, MeOH, 4 h, r.t. then Boc_2O, CPME, 16 h, RT; (iv) trimethyl phosphonoacetate, K_2CO_3, MeOH, 4 h 0 °C; (v) Amberlyst® 15, MeOH, 48 h, RT.

A plausible reaction mechanism for the cyclization of hydrazone **2a** is proposed in Scheme 4. The *N,N*-dialkylhydrazone group of **2a** could promote the acid-mediated elimination of the adjacent hydroxyl to give vinyldiazenium intermediate **13**.[22] Cyclization of this intermediate would give THF **3a** as either an *anti*- or *syn*-diastereoisomer. Resubmission of an isomerically pure sample of *anti*-**3a** to the reaction conditions resulted in the same 75:25 mixture of *anti*- and *syn*-diastereoisomers that is observed in the original reaction, which suggests that the diastereoselectivity is under thermodynamic control. Conducting the reaction in MeOH-d_4 did not result in the measurable incorporation of deuterium adjacent to the hydrazone, indicating that epimerization occurs through a reversible ring closure rather than *via* a vinylhydrazine intermediate. The proposed mechanism is also consistent with the observation that hydrazones **2a** and **2b** converge to THF **3a** and *ent*-**3a** with the same diastereoselectivity (Table 1, entries 1 and 2), as the two reactions would proceed through enantiomeric vinyldiazenium intermediates. Without TFA present no reaction was observed.



Scheme 5. Postulated mechanism and mechanistic studies.

In a preliminary study, the extension of this approach to hexoses was explored. Hydrazone **14**, formed from D-galactose, was treated was subjected to the TFA-mediated cyclization conditions. This gave a 60:40 mixture of THF **15** and tetrahydropyran **16** in 53% isolated yield, with both heterocycles formed as single stereoisomers.



Scheme 2. Extending the methodology to D-galactose. Reagents and conditions; 20 mol% TFA.

In summary, we have developed an efficient multi-gram approach to low-molecular weight chiral molecules from biomass feedstock. This route allows access to a range of THF products without the need for protecting groups, including a formal synthesis of 3*R*-3-hydroxymuscarine. On the basis of experimental evidence, we have also proposed a reaction mechanism for the key cyclization which is based on an unusual vinylhydrazine intermediate.

Experimental Section

Experimental procedures, ^{1}H and ^{13}C NMR spectra, characterization data of all compounds and XRD crystallography files are available in the supporting information.

A stirring mixture of hydrazone **2a** (20.0 g, 104 mmol) in methanol (210 mL, 0.5 M) was treated with TFA (1.5 mL, 2.4 g, 20 mol%) at room temperature and the reaction stirred at 40 °C for 16 h. The reaction was then quenched with aq. sat. $NaHCO_3$ and concentrated *in vaccuo* to give the crude hydrazone (*anti*:*syn* = 75:25). This was purified by flash column chromatography (80:100 hexane:acetone) to give THF **3a** (11.9 g, 68.3 mmol, 66%).

***THF anti*-3a:** Isolated as a single stereoisomer following recrystallization from boiling CPME. Isolated as a white crystalline solid; m.p. = 65–67 °C; R_f = 0.33 (1:1 acetone:hexane); ν_{max} (film/cm^{-1}) 3415s br. 2875s, 1586s, 1467s, 1445s; ^{1}H NMR (600 MHz; MeOH-d_4) 6.51 (1H, d, *J* = 6.6, N=C*H*), 4.23–4.18 (2H, m, N=CHC*H*, CH_2CH), 4.08 (1H, dd, *J* = 9.6, 4.9, OC*H*H'), 4.02 (1H, dd, *J* = 7.3, 5.1, N=CHCHC*H*), 3.76–3.72 (1H, m, OCH*H*'), 2.79 (6H, s, $N(CH_3)_2$); ^{13}C NMR (150 MHz; MeOH-d_4) 135.6 (*C*=N), 82.5 ($CHCH_2$), 76.5 (N=CHCH*C*H), 73.9 (OCH_2), 72.4 (CH_2CHCH), 42.8 ($N(CH_3)_2$); HRMS (EI^+) found $[M+H]^+$ 174.0979; $C_7H_{14}N_2O_3$ requires 174.0999; $[\alpha]_D$ (20 °C) = +85.8 (*anti*-**3a**, MeOH, C = 1.4).

***THF syn*-3a**: ^{1}H NMR (600 MHz; MeOH-d_4) 6.71 (1H, d, *J* = 7.2, N=C*H*), 4.36–4.31 (2H, m, N=CHC*H*; CH_2CH), 4.15 (1H, t, *J* = 4.8, C*H*$CHCH_2$), 3.91 (1H, dd, *J* = 8.7, 6.2, OC*H*H'), 3.76–3.72 (1H, m, OCH*H*'), 2.79 (6H, s, $N(CH_3)_2$); ^{13}C NMR (150 MHz; MeOH-d_4) 135.6 (*C*=N), 83.1 ($CHCH_2$), 74.3 (N=CHCH*C*H), 73.2 (N=CH*C*H), 72.5 (OCH_2), 42.8 ($N(CH_3)_2$).

Acknowledgements

This work was supported by GlaxoSmithKline (Industrial CASE Award) and the UCL PhD program in Drug Discovery.

Keywords: Biomass, Tetrahydrofuran, Hydrazone, Arabinose

[1] C. O. Tuck, E. Pérez, I. T. Horváth, R. A. Sheldon, M. Poliakoff, *Science* **2012**, *337*, 695-699.

[2] G. W. Huber, A. Corma, *Angewandte Chemie International Edition* **2007**, *46*, 7184-7201; P. N. R. Vennestrøm, C. M. Osmundsen, C. H. Christensen, E. Taarning, *Angewandte Chemie International Edition* **2011**, *50*, 10502-10509; J. Zakzeski, P. C. A. Bruijnincx, A. L. Jongerius, B. M. Weckhuysen, *Chemical Reviews* **2010**, *110*, 3552-3599; M. He, Y. Sun, B. Han, *Angewandte Chemie International Edition* **2013**, *52*, 9620-9633; P. Gallezot, *Chemical Society Reviews* **2012**, *41*, 1538-1558; S. A. Sanchez-Vazquez, H. C. Hailes, J. R. G. Evans, *Polymer Reviews* **2013**, *53*, 627-694.

[3] R. A. Sheldon, *Green Chemistry* **2014**, *16*, 950-963.

[4] M. Bayashi, K. Funane, H. Ueyama, S. Ohya, M. Tanaka, Y. Kato, *Bioscience, Biotechnology, and Biochemistry* **1993**, *57*, 998-1000; S. Kuhnel, H. Schols, H. Gruppen, *Biotechnology for Biofuels* **2011**, *4*, 14.

[5] J. J. Bozell, G. R. Petersen, *Green Chemistry* **2010**, *12*, 539-554; M. Spagnuolo, C. Crecchio, M. D. Pizzigallo, P. Ruggiero, *Biotechnol Bioeng* **1999**, *64*, 685-691.

[6] B. Li, S. Varanasi, P. Relue, *Green Chemistry* **2013**, *15*, 2149-2157.

[7] A. Corma, S. Iborra, A. Velty, *Chemical Reviews* **2007**, *107*, 2411-2502; L. Hu, G. Zhao, W. Hao, X. Tang, Y. Sun, L. Lin, S. Liu, *RSC Advances* **2012**, *2*, 11184-11206.

[8] P. F. Koh, P. Wang, J. M. Huang, T. P. Loh, *Chemical Communications* **2014**, *50*, 8324-8327.

[9] P. Srihari, Y. Sridhar, *European Journal of Organic Chemistry* **2011**, *2011*, 6690-6697.

[10] J. Eron, Jr., P. Yeni, J. Gathe, Jr., V. Estrada, E. DeJesus, S. Staszewski, P. Lackey, C. Katlama, B. Young, L. Yau, D. Sutherland-Phillips, P. Wannamaker, C. Vavro, L. Patel, J. Yeo, M. Shaefer, *The Lancet*, *368*, 476-482; J. Hao, B. Chen, Y. Yao, M. Hossain, T. Nagatomo, H. Yao, L. Kong, H. Sun, *Bioorganic & Medicinal Chemistry Letters* **2012**, *22*, 3441-3444; L. P. Jordheim, D. Durantel, F. Zoulim, C. Dumontet, *Nat Rev Drug Discov* **2013**, *12*, 447-464.

[11] K. Asano, S. Matsubara, *Journal of the American Chemical Society* **2011**, *133*, 16711-16713; D. Belmessieri, A. de la Houpliere, E. D. D. Calder, J. E. Taylor, A. D. Smith, *Chemistry – A European Journal* **2014**, *20*, 9762-9769; J. Lee, J. S. Panek, *The Journal of Organic Chemistry* **2015**, *80*, 2959-2971; N. Cox, M. R. Uehling, K. T. Haelsig, G. Lalic, *Angewandte Chemie International Edition* **2013**, *52*, 4878-4882; I. Čorić, J. H. Kim, T. Vlaar, M. Patil, W. Thiel, B. List, *Angewandte Chemie International Edition* **2013**, *52*, 3490-3493.

[12] K. M. Tomczyk, P. A. Gunka, P. G. Parzuchowski, J. Zachara, G. Rokicki, *Green Chemistry* **2012**, *14*, 1749-1758.

[13] M. Cifonelli, J. A. Cifonelli, R. Montgomery, F. Smith, *Journal of the American Chemical Society* **1955**, *77*, 121-125; I. Lundt, H. Frank, *Tetrahedron* **1994**, *50*, 13285-13298; L. M. H. Leung, V. Gibson, B. Linclau, *Tetrahedron: Asymmetry* **2005**, *16*, 2449-2453; S.-M. S. Choi, P. M. Myerscough, A. J. Fairbanks, B. M. Skead, C. J. F. Bichard, S. J. Mantell, J. C. Son, G. W. J. Fleet, J. Saunders, D. Brown, *Journal of the Chemical Society, Chemical Communications* **1992**, 1605-1607.

[14] G. J. Ewing, M. J. Robins, *Organic Letters* **1999**, *1*, 635-636; D. Rolf, G. R. Gray, *Journal of the American Chemical Society* **1982**, *104*, 3539-3541.

[15] T. Saloranta, R. Leino, *Synlett* **2015**, *26*, 421-425; I. S. Young, P. S. Baran, *Nat Chem* **2009**, *1*, 193-205.

[16] R. Lazny, A. Nodzewska, *Chemical Reviews* **2010**, *110*, 1386-1434.

[17] M. Koóš, H. S. Moscher, in *Collect. Czech. Chem. Commun., Vol. 50*, **1985**, pp. 1994–1999 ; M. Behforouz, J. L. Bolan, M. S. Flynt, *The Journal of Organic Chemistry* **1985**, *50*, 1186-1189.

[18] R. K. Henderson, C. Jimenez-Gonzalez, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, A. D. Curzons, *Green Chemistry* **2011**, *13*, 854-862.

[19] CCDC 1411520 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

[20] In deuterium oxide compound **5** existed as an 85:15 mixture of hydrates, with a structure analogous to that drawn in Scheme 4 (accounting for deuterium exchange) However NMR spectra in MeOH-d_4 and DMSO-d_6 indicated a more complex mixture of compounds, possibly as a result of reversible oligomerization. See Supporting Information for details.

[21] S. J. Mantell, P. S. Ford, D. J. Watkin, G. W. J. Fleet, D. Brown, *Tetrahedron* **1993**, *49*, 3343-3358.

[22] F. W. Lichtenthaler, T. Weimer, S. Immel, *Tetrahedron: Asymmetry* **2004**, *15*, 2703-2709.

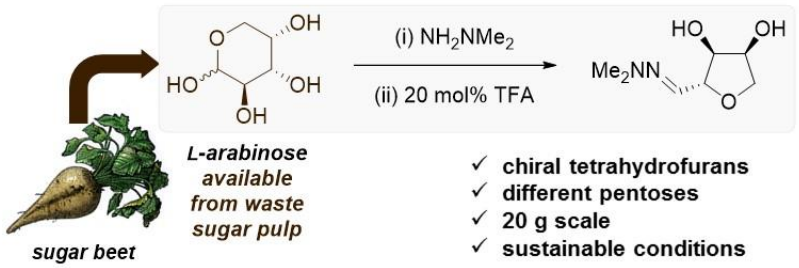
Entry for the Table of Contents

COMMUNICATION

Robert W. Foster, Christopher J. Tame, [1] Dejan-Krešimir Bučar Helen C. Hailes and Tom D. Sheppard

Page No. – Page No.

The Sustainable Synthesis of Small Chiral Tetrahydrofurans from Waste Carbohydrate Feedstock



Sweet pickings. L-Arabinose, a major component of sugar beet pulp, was converted into a chiral tetrahydrofuran through use of an unusual hydrazone-mediated cyclization. This approach was developed for the stereoselective synthesis of diverse small-molecule tetrahydrofurans from biomass feedstock sources, without the use of protecting groups.